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4- and 6-Hydroxy-2,3-diphenylindole and 2,3-diphenylindole-4,7- and -6,7-quinone. By BARBARA CLIFFORD, PATRICIA NIXON, CHARLOTTE SALT, and MURIEL TOMLINSON

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439. *Chlorine Activation by Redox-transfer. Part I. The Reaction between Aliphatic Amines and Carbon Tetrachloride.*

By M. Asscher and D. Vofsi.

A free-radical chain mechanism is suggested for the reaction between aliphatic amines and carbon tetrachloride catalysed by copper chloride. According to this mechanism, the amine is chlorinated by carbon tetrachloride to an α-chloro-amine. Chloroform is the second product. Unchanged amine eliminates hydrogen chloride from the α-chloro-amine, producing amine hydrochloride. Copper ions appear to function as chlorine-atom carriers, providing a pathway for chain transfer. The effect of this "redox-transfer" appears as an enhanced apparent reactivity of carbon tetrachloride.

Reaction between carbon tetrachloride and aliphatic amines is already known;[1-3] strong catalysis by copper and cupric salts was noted by Foster and his co-workers.[3a] This observation is now confirmed for a series of primary, secondary, and tertiary amines, and a more detailed study made of the ethanolamines; catalysis by ferric and ferrous chloride was also noted. The possibility that this reaction may proceed *via* a free-radical chain mechanism is supported by the following: (*a*) On addition of traces of cupric and cuprous chloride to a solution of triethanolamine and carbon tetrachloride in methanol, at room temperature, there is a well-defined induction period (also in a thoroughly degassed system), during which the initially blue solution becomes green. The onset of reaction can be seen by the appearance of a precipitate of amine hydrochloride and a rise in the temperature. (*b*) The reaction induces the addition of carbon tetrachloride to aliphatic olefins, which is known to be a free-radical chain process.[4] (*c*) The reaction can be inhibited by small amounts of styrene.

These observations and the formation of chloroform and amine hydrochloride as main products can be accounted for by assuming a mechanism consisting of the following elementary steps:

Initiation	$Cu^{2+} + R{\cdot}CH_2{\cdot}NR'R'' \longrightarrow Cu^{+} + R{\cdot}\dot{C}H{\cdot}NR'R'' + H^{+}$	(1)
Propagation	$Cu^{+} + CCl_4 \longrightarrow Cu^{+}(Cl) + {\cdot}CCl_3$	(2)
	${\cdot}CCl_3 + R{\cdot}CH_2{\cdot}NR'R'' \longrightarrow CHCl_3 + R{\cdot}\dot{C}H{\cdot}NR'R''$	(3)
	$R{\cdot}\dot{C}H{\cdot}NR'R'' + Cu^{+}(Cl) \longrightarrow R{\cdot}CHCl{\cdot}NR'R'' + Cu^{+}$	(4)
Termination	$2R{\cdot} \longrightarrow$ products	(5)

The α-chloro-amine formed in stage (4) is extremely reactive towards nucleophiles[5] and will immediately react with excess of amine, ultimately eliminating hydrogen chloride to form the amine hydrochloride and coloured resins.[6,7] This scheme indicates that copper ions are necessary in the initiation as well as in the propagation steps. Their rôle in propagating the chain is inferred from the absence of any reaction when benzoyl peroxide is added instead of copper. The generation of benzoyloxy-radicals in presence of tertiary amines at room temperature has been demonstrated before.[6,8]

The inhibition of reaction by styrene is indicative that the trichloromethyl radical is

[1] Collins, *Chem. and Ind.*, 1957, 704; Sharada and Vasudeva Murthy, *Current Sci.*, 1960, **29**, 179.
[2] Beichl, Collwell, and Miller, *Chem. and Ind.*, 1960, 203.
[3] (*a*) Cromwell, Foster, and Wheeler, *Chem. and Ind.*, 1959, 228; (*b*) Foster, *Chem. and Ind.*, 1960, 1354.
[4] Kharasch, Jensen, and Urry, *J. Amer. Chem. Soc.*, 1947, **69**, 1100.
[5] Böhme, Lehners, and Keitzer, *Chem. Ber.*, 1958, **91**, 340; Böhme, Ellenberg, Herboth, and Lehners, *ibid.*, 1959, **92**, 1608.
[6] Horner and Schwenk, *Annalen*, 1950, **566**, 69; Horner, Brüggemann, and Knapp, *ibid.*, 1959, **626**, 1.
[7] Henbest and Slade, *J.*, 1960, 1558.
[8] Walling and Indictor, *J. Amer. Chem. Soc.*, 1958, **80**, 5814.

one of the chain carriers, since styrene is an efficient scavenger [9] for this radical. The resulting benzyl-type radical is apparently not chain-sustaining in the present case.

The individual steps of the above scheme are supported:

Step 2. It was shown by Doughty [10] that cuprous ion in aqueous ammonia is instantaneously oxidised by carbon tetrachloride at room temperature; a trichloromethyl radical and a chloride ion are initially presumably formed. In the presence of an amine, the same reaction probably occurs. The driving force is no doubt the high stability of cupric ion in co-ordination with amine or ammonia. Without amine, much higher temperatures are required for reaction (2) (unpublished results).

Step 3. The formation of chloroform as a major product is in accord with the ready abstraction by free radicals of α-hydrogen atoms from amines.[10a]

Step 4. Free radicals readily abstract halogen from cupric or ferric halides.[11,12,13] Entwistle [13a] pointed out that the donor-acceptor relation between radical and substrate can be of far greater importance for interactions between a radical and a metal halide than for ordinary homolytic displacements. The amine radical is probably one of the strongest donors known, owing to the great stability of the corresponding cation, as reflected by the salt-like nature of α-chloro-amines.[5] Therefore, very strong donor properties will be conferred both on amine as substrate in reaction (3), and on the amine radical. This will greatly facilitate reactions (3) and (4).[14]

The induction period in the reaction, catalysed by cupric chloride, between triethanolamine and carbon tetrachloride in methanol, can be eliminated by a small amount of ethanolamine hydrochloride. The colour of the solution is then green from the start.

Cuprous chloride, which according to reaction (2) should immediately generate trichloromethyl radicals and thus initiate the reaction, nevertheless shows an induction period in the absence of added hydrochloride. It appears, therefore, that a certain minimum concentration of chloride ions is needed for the reaction.

The following mobile equilibrium is established in the reaction medium:

$$\underset{\text{(I)}}{Cu^{2+}(\text{amine})(\text{solvent})} + Cl^- \rightleftharpoons \underset{\text{(II)}}{Cu^{+}(\text{amine})(\text{solvent})(Cl)} \quad \ldots\ldots\ldots \quad (6)$$

Complex (I) is blue and complex (II) green.[15] Apparently, a cupric complex ion like (II), with at least one chlorine bound to copper, is needed for step (4),[11] and perhaps also for step (1). In the presence of a large excess of amine and methanol, equilibrium (5) is displaced too far to the left, and chloride ions have to be furnished, or slowly produced during the induction period, in order to obtain a fast reaction. [In the reaction scheme we have written $Cu^+(Cl)$ instead of (II) for the sake of brevity.] Consistent with this view is the fact that in isopropyl alcohol or t-butyl alcohol, both of which solvate cupric ion much less than does methanol, the solution is green from the start and there is a much shorter induction period. Ethylenediaminetetra-acetic acid, on the other hand, has a pronounced retarding effect, for it is a strong sequestering agent for cupric ion.

We have no direct evidence for step (1), but it was reported [16] that cupric chloride is reduced by acetone in a reaction which is catalysed by chloride ions.

[9] Robb and Vofsi, *Trans. Faraday Soc.*, 1959, **55**, 566.
[10] Doughty, *J. Amer. Chem. Soc.*, 1919, **41**, 1131.
[10a] Bamford and White, *Trans. Faraday Soc.*, 1956, **52**, 716; Schenck and Zunft, *Angew. Chem.*, 1957, **69**, 595; Urry and Juveland, *J. Amer. Chem. Soc.*, 1958, **80**, 3322; Henbest and Patton, *J.*, 1960, 3557.
[11] Kumamoto, de la Mare, and Rust, *J. Amer. Chem. Soc.*, 1960, **82**, 1935.
[12] Bamford, Jenkins, and Johnston, *Proc. Roy. Soc.*, 1957, *A*, **238**, 214.
[13] (*a*) Entwistle, *Trans. Faraday Soc.*, 1960, **56**, 284; (*b*) Bamford, Jenkins, and Johnston, *Trans. Faraday Soc.*, 1959, **55**, 421.
[14] Walling, *J. Amer. Chem. Soc.*, 1948, **70**, 2561; "Free Radicals in Solution," Wiley, New York, 1957, p. 158; Russell, *J. Amer. Chem. Soc.*, 1956, **78**, 1047.
[15] Udovenko and Artemenko, *Zhur. neorg. Khim.*, 1959, **4**, 353.
[16] Kochi, *J. Amer. Chem. Soc.*, 1955, **77**, 5274; Dickerman, Weiss, and Ingberman, *J. Org. Chem.*, 1956, **21**, 380.

Step (4) is in itself a chain-breaking reaction,[11,12,13,17] but in conjunction with step (2) it provides a pathway for chain transfer. This mode of transfer, which we will call " redox-transfer," is brought about by copper or iron ions as chlorine-atom carriers, and manifests itself in a much greater apparent reactivity of carbon tetrachloride. Redox-transfer will in principle be possible only for compounds in which halogen is bound to a strongly electronegative group, for otherwise the vital step (2) will be reversed, as in step (4).

The net result of steps (4) and (2) is a normal homolytic displacement:

$$R{\cdot}\dot{C}H{\cdot}NR'R'' + CCl_4 \longrightarrow R{\cdot}CHCl{\cdot}NR'R'' + {\cdot}CCl_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Foster's results [3b] do not allow a conclusion as to whether step (7) can take place at room temperature, or whether traces of metal ions, which are not easily excluded, are responsible for the reaction which he observed between triethylamine and carbon tetrachloride.

Isopropyl alcohol, when used as a solvent for reaction between amine and carbon tetrachloride, is concurrently chlorinated by an entirely analogous redox-transfer mechanism, giving 2-chloropropan-2-ol, which immediately decomposes into acetone and hydrochloric acid.[18] This results in the formation of additional amine hydrochloride. t-Butyl alcohol, on the other hand, is an inert solvent, for it cannot be dehydrogenated by a trichloromethyl radical (see Experimental).

Experimental

Materials.—" AnalaR " carbon tetrachloride and triethanolamine (Eastman White Label) were used as supplied. Methanol was Fisher spectrograde product, and 1-octene a Phillips pure-grade material.

Reaction of Triethanolamine with Carbon Tetrachloride.—(a) *Detection of chloroform.* To a solution of triethanolamine (10 g., 0·067 mole) in isopropyl alcohol (20 g.) and carbon tetrachloride (10 g.) were added 10 drops of a 1·5% solution of cupric chloride dihydrate in isopropyl alcohol (≡2·5 mg. of $CuCl_2$). The reaction vessel was stoppered and kept at 25°. A precipitate began to appear after 6 min., and after 1 hr., water (200 c.c.) was added. The lower layer was separated and distilled (steam-bath). The distillate (8·4 g.) was analysed by gas-liquid chromatography at 38° (on silicone oil as the stationary phase, in a 1-m. column), and consisted of 33% chloroform, 61% carbon tetrachloride, and 6% acetone. Acetone is a product of the concurrent chlorination of isopropyl alcohol by carbon tetrachloride [see (b)].

(b) *Concurrent chlorination of triethanolamine and isopropyl alcohol.* The experiment was carried out as in (*a*). After 1 hr., the precipitate which had formed was sucked off, washed with isopropyl alcohol and acetone, and dried for 12 hr. at 70° (Found: Cl, 19·4. Calc. for triethanolamine hydrochloride: Cl, 19·1%), m. p. and mixed m. p. 178—180° (lit., m. p. 177°). The yield of hydrochloride before recrystallisation was 7·05 g. (=0·038 mole), 13% in excess of the theoretical yield. This excess reflects the extent to which isopropyl alcohol has been chlorinated by carbon tetrachloride in the presence of amine.

When the same reaction was carried out in t-butyl alcohol, and catalysed by a 1·5% solution of cupric chloride in t-butyl alcohol, 98·5% of the theoretical yield of the salt (Found: Cl, 19·4%) was obtained.

(c) *Variables affecting the induction period.* To a mixture (10 g.) of equal weights of triethanolamine, carbon tetrachloride, and methanol was added cupric chloride dihydrate (4 mg.). After 15 min. the blue solution became green, and the hydrochloride began to precipitate. After 20 min. the solution began to boil. When ferrous chloride tetrahydrate (14 mg.) was used instead of cupric chloride, precipitation began without an induction period, but the reaction was slower and less exothermic. When to the same amount of mixture, ethanolamine hydrochloride (30 mg.) was added, and thereafter 3 drops of a 2·5% solution of cupric chloride dihydrate in methanol (≡1 mg. of chloride), the solution immediately became faintly green and warmed, as triethanolamine hydrochloride began to precipitate, again without an induction period. When ethanolamine hydrochloride was omitted and 8 drops of the same methanolic cupric chloride solution were added, there was an induction period of 55 min. When instead

[17] Kochi, *J. Amer. Chem. Soc.*, 1956, **78**, 4815.
[18] Razuvaev, Moryganov, and Volkova, *Zhur. obshchei Khim.*, 1955, **25**, 495.

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of methyl alcohol, isopropyl alcohol or t-butyl alcohol was taken as the solvent, the precipitation of the salt started almost immediately on addition of cupric chloride.

Reaction between 1-Octene and Carbon Tetrachloride in the Presence of Ethanolamine.—Cupric chloride dihydrate (50 mg.) in t-butyl alcohol (10 g.) was added to a mixture of ethanolamine (3 g.), oct-1-ene (28 g., 0·25 mole), carbon tetrachloride (77 g., 0·5 mole), and t-butyl alcohol (20 g.), and the blue solution was refluxed for 10 hr. After cooling, the mixture was poured into 0·5 l. of water, the lower layer separated, and the aqueous layer extracted twice with carbon tetrachloride and discarded. The extracts were added to the separated lower layer, washed twice with water, and dried ($CaCl_2$). The solvent was removed by distillation and the residue distilled; unchanged oct-1-ene (5 g.) was collected (b. p. 35—40°/25 mm.), followed by a fraction (42 g.) of b. p. 80—105°/0·3 mm. (bath up to 160°); a brown oily residue (9·2 g.) remained, presumably mostly an adduct of 2 moles of oct-1-ene to 1 mole of carbon tetrachloride. The fraction, b. p. 80—105°/0·3 mm., was redistilled: it had b. p. 78—80°/0·3 mm. (Found: Cl, 51·5, 51·7. Calc. for 1,1,1,3-tetrachlorononane: Cl, 53·3%). A vapour-phase chromatogram showed that the product (77%) was almost homogeneous.

Reaction of Ethylene and Carbon Tetrachloride[19] *in the Presence of Triethanolamine.*—A 100-c.c. stainless-steel autoclave, fitted with a magnetic stirrer, was charged with triethanolamine (4 g.), methyl alcohol (20 g.), carbon tetrachloride (60 g.), and cupric bromide (66 mg.). Without previous purging, the vessel was left for 1½ hr. under an ethylene pressure of 61 atm., while the contents were stirred. The ethylene source was disconnected and stirring continued during 65 hr. at room temperature. After release of the excess of ethylene and opening of the autoclave, the solution was filtered from the precipitate of triethanolamine hydrochloride (2·9 g.) and freed from methanol and excess of carbon tetrachloride by distillation at atmospheric pressure (bath temperature up to 140°). Distillation was continued up to 180° (bath) at 25 mm. and up to 140° (bath) at 0·3 mm. The combined distillate (58·1 g.) was analysed by gas–liquid chromatography at 200° on silicone oil as the stationary phase, in a 0·76-m. column; it consisted of 3% of 1,1,1,3-tetrachloropropane, 44% of 1,1,1,5-tetrachloropentane, 36% of 1,1,1,7-tetrachloroheptane, 14% of 1,1,1,9-tetrachlorononane and 3% of 1,1,1,11-tetrachloroundecane. Conversion of carbon tetrachloride was 65%.

The authors are indebted to Professor A. Katchalsky for advice and interest.

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REHOVOTH, ISRAEL. [*Received, July 11th*, 1960.]

[19] Joyce, Hanford, and Harmon, *J. Amer. Chem. Soc.*, 1948, **70**, 2529; Bolt and Joyce, *Chem. Eng. News*, 1947, **25**, 1866; Nesmeyanov, Freidlina, *et al.*, *Quart. Rev.*, 1956, **10**, 333.

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440. *The Chemistry of the Bile Pigments. Part II.*[1] *The Preparation and Spectral Properties of Biliverdin.*

By C. H. GRAY, A. LICHTAROWICZ-KULCZYCKA, D. C. NICHOLSON, and, in part, Z. PETRYKA.

The absorption spectrum, between 250 and 700 mμ, of pure biliverdin has been determined for methanol, chloroform, and methanolic hydrogen chloride solutions. The position and molecular extinction coefficients of the absorption maxima differ from those reported by other workers whose preparations of biliverdin were probably contaminated with violinoid pigments and residual bilirubin.

THE absorption spectrum of biliverdin in neutral solutions is reported (see Table 1) to show a band between 380 and 400 mμ (ε 28,000) and a broad maximum at about 640—665 mμ (ε 15,000). In hydrochloric acid or in methanolic hydrogen chloride, hydrochloride formation increases absorption of both bands and causes a bathochromic shift of the maximum in the visible region, together with a slight hypsochromic shift of the maximum

[1] Part I, Gray and Nicholson, *J.*, 1958, 3085.

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in the ultraviolet region. In the present study, the absorption spectrum of specially purified biliverdin in chloroform, methanol, and methanolic hydrogen chloride has been determined. The positions of the maxima, the molecular extinction coefficients at these maxima, and the ratio of these coefficients, as found by us, do not agree with those reported by others.

TABLE 1. *Previous spectroscopic data for biliverdin.*

$\lambda_{max.}$ (mμ)		E_2/E_1	$\lambda_{min.}$ (mμ)	Remarks	Ref.
			MeOH solutions		
640 (10·4)	392 (25·0)	2·43	480		*a*
640	390—400	2·46	500	Infl. 560 mμ	*b*
			$CHCl_3$ solutions		
640	380	2·44	500		*b*
640	390	2·73			*c*
		2·91			
660	380	3·95	480	Absorption increased below 350 mμ	*d*
665 (15·8)	384 (52·5)	3·31	490 (2·2)	Secondary max. 316 (24·0) & 282 mμ (19·5)	*e*
			Solutions in 5% HCl–MeOH		
680 (28·0)	377 (48·0)	1·72	510		*a*
680	375	2·89	495		*c*
680—690	370	3·91	470	Absorption below 350 mμ increases	*d*
665	384		490		*e*

Figures in parentheses give millimolar extinction coefficients where available; E_2/E_1 is the calculated ratio of the absorption at the two maxima, from reported data.

References: (*a*) Ref. 4. (*b*) Sakamoto, *Acta Med. Okayama*, 1956, **10**, 11. (*c*) *Idem*, *ibid.*, p. 47. (*d*) Fox and Milliott, *Experientia*, 1954, **10**, 185. (*e*) Tixier, *Ann. Inst. Oceanogr.*, 1945, **22**, 361, for the dimethyl ester (same figures obtained for dioxan solutions).

Biliverdin was obtained by the ferric chloride oxidation of bilirubin, Lemberg's method [2] being modified to facilitate the elimination of traces of residual bilirubin and oxidation products of biliverdin. This material gave the values shown in Tables 2 and 3.

During the first half-hour after the preparation of the solutions the maximum in the red region was broad and its position difficult to define: often two close maxima were detected. This was probably due, in spite of our attempts at complete purification, to the partial formation of a metal complex, the absorption maximum of which [3] is at 695 mμ, and near that of the free pigment. After a few hours in the dark, the intensity of absorption was unchanged but the maximum became more clearly defined at about 640 mμ, so that the

TABLE 2. *Our absorption data of biliverdin and its hydrochloride.*

Solvent	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$	E_2/E_1
MeOH	640—650	12·9	375—380	40·5	3·13
$CHCl_3$	640—650	13·4	378—380	41·7	3·12
HCl–MeOH (5% w/v)	665—670	23·3	372·5	47·3	2·05
0·2N-HCl in MeOH	670	22·8	375	47·4	2·08
0·6N- ,, ...	660—670	23·2	375	46·2	2·00
1·1N- ,, ...	660—675	22·9	375	47·1	2·03
1·9N- ,, ...	665—670	22·9	375	45·6	1·99
2·8N- ,, ...	660—680	22·9	375	45·5	2·00
5·9N- ,, ...	670—685	23·0	375—380	45·2	1·98
Mean values for acidic solutions	660—680	23·0	370—380	46·35	2·02

wavelength readings were reproducible. The maximum at 375 mμ remained unchanged. Spectra of solutions with pH values between 4·4 and 6·9 were almost identical and showed no hydrochloride formation. At pH of about 2, most of the pigment was present as the hydrochloride, as was shown by the ratio of the optical density at 375 to that at 670 mμ. In more acid solutions (see Table 2) the hydrochloride was formed immediately; the molecular extinction coefficients were then independent of the concentration of the acid.

[2] Lemberg, *Annalen*, 1932, **499**, 25.
[3] Part III, following paper.

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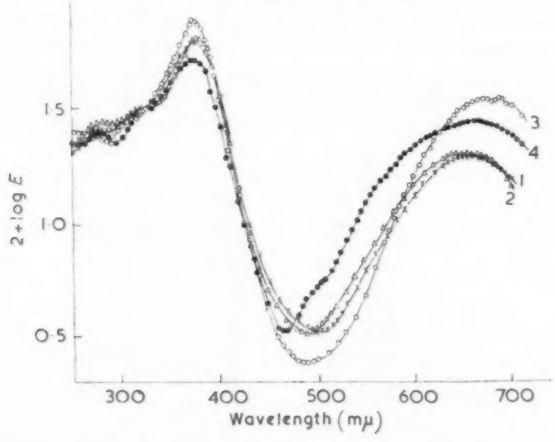
TABLE 3. *Absorption of biliverdin in weakly acidic methanolic solutions after different times.*

pH of solvent	pH of soln.	$\lambda_{max.}$ (mμ)	E_1	$\lambda_{max.}$ (mμ)	E_2	E_2/E_1
			0·25 *Hr. after dissolution*			
7·0	6·9	670	0·238	377·5	0·731	3·08
6·0	5·4	685	0·255	377·5	0·765	3·00
5·0	5·6	675	0·249	375·0	0·726	2·99
4·0	5·0	660	0·246	375·0	0·734	2·99
3·0	4·4	670	0·241	375·0	0·724	3·00
2·0	2·1	670	0·427	372·5	0·914	2·14
			16 *Hr. after dissolution.*			
7·0	6·8	640	0·242	377·5	0·730	3·07
6·0	6·2	640	0·243	377·5	0·714	2·94
5·0	6·0	665	0·244	377·5	0·712	2·92
4·0	5·5	665	0·238	375·0	0·712	2·94
3·0	5·1	640	0·241	375·0	0·674	2·79
2·0	2·4	675	0·412	372·5	0·919	2·23
			40 *Hr. after dissolution*			
7·0	6·8	635	0·279	372·5	0·604	2·17
6·0	6·3	640	0·256	375·0	0·691	2·70
5·0	6·3	635	0·284	375·0	0·617	2·18
4·0	6·7	640	0·246	375·0	0·670	2·72
3·0	5·3	635	0·281	375·0	0·614	2·19
2·0	2·2	680	0·417	372·5	0·905	2·17

The values for the spectroscopic constants of biliverdin (see Table 1) have been reported previously for 5% methanolic hydrochloric acid solutions but it is not clear whether anhydrous hydrogen chloride or concentrated hydrochloric acid was used. The light absorption

Absorption spectra of biliverdin: 1, *in* MeOH; 2, *in* $CHCl_3$; 3, *in* MeOH–HCl; 4, *in* MeOH–HCl *after solution had been kept for 2 hr. in sunlight.*



was, therefore, also measured in methanol containing 5% by weight of concentrated hydrochloric acid and was the same as that of a solution of methanol containing 5% (w/v) hydrogen chloride. Fig. 1 shows the absorption curves of free biliverdin in methanol and in chloroform, and of the hydrochloride in methanolic hydrogen chloride. Even when the vessels were stoppered and stored in the dark, oxidation of biliverdin occurred (see Table 3). The oxidation was accelerated by exposure to light and air and occurred more readily in acid methanol than in chloroform. Visually the solution appeared more

blue: spectroscopically there was a decrease of absorption at 375 mμ, the maximum at 670 mμ decreasing less and being shifted to lower wavelength. There was an increase of absorption in the 470—630 mμ region and new maxima appeared at ~270 and 315 mμ. The minimum at 480—500 mμ shifted to 470—480 mμ. The ratio of the intensity of absorption at the two main maxima (E_{375}/E_{670}) decreased and approached the value calculated from previously published data (Table 1). These changes are shown in curves 3 and 4 of Fig. 1.

Lemberg's absorption curves for biliverdin in methanol [4] reveal the presence of bilirubin in his pigment, for there is increased absorption at 490—530 mμ and the lower absorption band is at 392 mμ instead of 370—380 mμ. Traces of bilirubin in biliverdin hydrochloride are readily oxidised to the latter and catalyse the further oxidation of biliverdin to violinoid pigments.[5] Such impurities in Lemberg's hydrochloride are revealed by a ratio for E_{375}/E_{670} of 1·71 instead of 2·2. These changes in the spectra of ageing solutions of biliverdin are paralleled by similar changes in the spectra of its zinc complex (see Part III [3]). The effect of change in pH on the spectra of verdins is reported in Part IV of this series.[6]

Experimental

Chloroform was freed from acid by distillation over potassium carbonate. Peroxide-free ether was used. Oxygen-free nitrogen was obtained by passing the gas through three lots of alkaline sodium dithionite solution.[7]

Preparation of Pure Bilirubin.—Bilirubin from two sources was used. (*a*) Fresh pig's bile (2 l.) was mixed with aqueous 0·1N-sodium hydroxide (3 l.) and left for 24 hr. for hydrolysis of conjugates of bilirubin. After acidification to Congo Red with 11N-hydrochloric acid, the mixture was extracted with chloroform (15 × 500 ml.). The extracts were washed with water and dried by filtration. Removal of the solvent under reduced pressure afforded crude bilirubin (1·6 g.), which was continuously washed with ether and then with methanol in a Soxhlet extractor until the washings were colourless. The pigment was then washed with methanol, extracted into chloroform, recovered, and crystallised. Continuous extraction with ether and methanol and crystallisation from chloroform were then repeated three times. Pure bilirubin was thus obtained in excellent yield (418 mg.). Recorded yields are 8 mg.[8] and 13·2 mg.[9]/100 ml. of pig's bile and 16·5 mg./100 ml. of human bile.[10]

(*b*) Commercial bilirubin (from Messrs. Light & Co.), although of high molecular extinction coefficient, contained impurities of the meso-type, for ethylmethylmaleinimide was obtained on oxidation by nitric acid. These impurities were eliminated by washing the material with ether and methanol successively in a Soxhlet apparatus. The final product was crystallised from chloroform.

The two bilirubin preparations showed ε 55,600 at 450 mμ in chloroform and behaved identically; both were shown to be free from mesobilirubin and other meso-pigments by demonstrating the absence of ethylmethylmaleinimide in the products of oxidation by nitric acid (see Part III [3]).

Preparation of Biliverdin.—The purified bilirubin (150 mg.) in methanol (200 ml.) was refluxed with a 20% solution of ferric chloride in 10N-hydrochloric acid (10 ml.) on a water-bath for 0·5 hr. The solution was cooled, filtered from residual bilirubin, and neutralised by addition of saturated aqueous sodium acetate. The mixture was extracted with ether (3 × 100 ml.), and the combined extracts were washed with 2N-sodium acetate and with water and were extracted with N-hydrochloric acid (3 × 100 ml.). The pigment present in the acid was removed in chloroform (3 × 100 ml.), which was then washed with water (5 × 100 ml.) to liberate the free pigment. The chloroform solution was dried by filtration and evaporated to

[4] See Lemberg and Legge, "Haematin Compounds and Bile Pigments," Interscience Publ. Inc., New York, 1949, p. 117.
[5] Kulczycka, unpublished observations.
[6] Part IV, Gray, Kulczycka, and Nicholson, *J.*, 1961, 2276.
[7] Linstead, Elvidge, and Whalley, "Modern Techniques of Organic Chemistry," Butterworths, London, 1955, p. 139.
[8] Gibson and Lowe, *J. Biol. Chem.*, 1938, **124**, xii.
[9] U.S.P. 2,386,716/1945.
[10] Libowitzky, *Z. physiol. Chem.*, 1940, **263**, 267.

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dryness under reduced pressure. The biliverdin was dissolved in the smallest possible quantity of methanol (10 ml.), leaving a residue of bilirubin. The biliverdin obtained by evaporation of the methanol solution was washed with light petroleum (b. p. 40—60°; 2 × 50 ml.) to remove traces of oxidation products. The residue was washed with ether and crystallised from methanol under nitrogen, to give pure biliverdin (48 mg.). Chromatography of a portion on chalk and elution with 20 : 1 light petroleum (b. p. 40—60°)–chloroform proved its homogeneity and this was confirmed spectroscopically.

To increase the yield it is possible to extract additional crude biliverdin from the ether solution by further extraction with 1N- and 2·8N-hydrochloric acid.

Rapidity of work, protection from air and strong light, and exclusion of oxygen from reagents are necessary in the above preparation if the production of further oxidation products is to be avoided. When these conditions are fulfilled, the proportion of pigment requiring extraction with 2·8N-hydrochloric acid is negligible.

Measurements of Absorption (with Z. PETRYKA).—" AnalaR " methanol (pH 8·05) was used for the preparation of all solutions. Solutions of hydrogen chloride in methanol were prepared by dilution of a saturated methanolic solution of gas with methanol. Normality of these solutions was determined by titration against standard alkali. The pH of the weakly acid solutions was measured on an E.I.L. 23A type of pH meter, standardised with 0·05M-potassium hydrogen phthalate (pH 4·00) and 0·05M-sodium tetraborate (pH 9·07). A standard solution of biliverdin in chloroform was prepared. 0·3488 mg. quantities of biliverdin were obtained by evaporation of appropriate volumes of the standard solution and were stored under nitrogen. Approximately 0·5 hr. before spectrophotometry each residue was dissolved in 25 ml. of appropriate solvent, and the vessel was stoppered and stored in the dark. Measurements were carried out in 1 cm. stoppered quartz cells in a Hilger spectrophotometer (type H 700). Wavelength settings and optical-density readings were checked with a calibrated rhodiumised quartz filter, and the former were confirmed by using a chloroform solution of stercobilin ($\lambda_{max.}$ 496 mμ) and a calibrated didymium filter. The pH's of the dilute acid solutions were also measured after spectrophotometry on the pH-meter. Within the narrow range of concentrations used the solutions obeyed Beer's law (E 0·2—1·0).

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441. *The Chemistry of the Bile Pigments. Part III.*[1] *Prototropy of Bilirubin to a Verdinoid Pigment.*

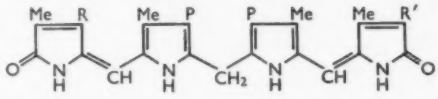
By C. H. GRAY, A. KULCZYCKA, and D. C. NICHOLSON.

Treatment of bilirubin with alkoxides in the absence of oxygen affords a pigment spectroscopically similar to dihydrobiliverdin and containing a β-ethyl-β-methylpyrrole ring. Evidence is presented that the change is prototropic. Spectral absorption studies of verdins and their zinc complexes are reported.

TAUTOMERISATION in bile pigments has been postulated to explain certain stages in the Gmelin reaction,[2] the weakly basic behaviour of bilirubin, which is unable to form complex salts,[3] the temperature-dependence of partition of purpurins between organic solvents and acids,[4] some properties of stercobilin,[5] formation of metal complexes by the dimethyl ether

[1] Part II, preceding paper.
[2] Fischer and Orth, " Die Chemie des Pyrrols," Akademische Verlagsges., Leipzig, 1937, p. 715.
[3] Lemberg and Legge, " Haematin Compounds and Bile Pigments," Interscience Publ., Inc., New York, 1949, pp. 108, 119.
[4] Ref. 3, p. 132.
[5] Gray and Nicholson, *Nature*, 1957, **179**, 264.

of mesobilirubin,[6] conversion of mesobiliviolin into mesobilirubin,[7] the anaerobic conversion of d-urobilin into violinoid pigments,[8] and differences in behaviour of d- and i-urobilin on treatment with ferric chloride.[9] Of these examples, only the last two are isomerisations

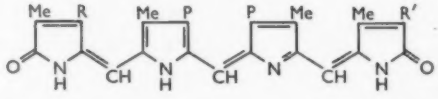


(Ia) R = R′ = CH:CH$_2$ (Ic) R = CH:CH$_2$; R′ = Et

(Ib) R = R′ = Et (Id) R = Et; R′ = CH:CH$_2$

involving the β-side chains of the pigments concerned. In this paper evidence is reported for the prototropic converson of a bisvinylrubin (bilirubin) into a monoethylmonovinylverdin (dihydrobiliverdin).

Rubins are bile pigments (I) containing two oxodipyrrylmethene units linked by a central methylene group. Bilirubin and mesobilirubin have structures (Ia and b respectively).[10] Dihydrobilirubin probably has structure (Ic)[11] but (Id) cannot be excluded.



(IIa) R = R′ = CH:CH$_2$ (IIc) R = CH:CH$_2$; R′ = Et

(IIb) R = R′ = Et (IId) R = Et; R′ = CH:CH$_2$

Biliverdin and mesobiliverdin (glaucobilin), with four conjugated pyrrole rings instead of two independent pairs, have the structures (IIa and b respectively).[12,13] Dihydrobiliverdin has not previously been described and may have either of the structures (IIc and d).

The bilirubin (10^{-3} ε = 56·6 at 450 mμ in chloroform) used in these experiments was free from pigments containing β-ethyl groups, because ethylmethylmaleinimide could not be detected after oxidation with nitric acid. Treatment of this bilirubin with boiling ethanolic sodium ethoxide in the absence of oxygen produced a verdinoid pigment which differed from the original bilirubin in containing a β-ethyl-β-methylpyrrole component, as shown by the formation of ethylmethylmaleinimide on oxidation. The isolation of this imide from the oxidation products of bilirubin treated with alkoxide has been reported previously.[14]

Since the verdinoid pigment was produced from bilirubin under conditions in which oxidation was excluded, its formation must be an isomerisation; mechanisms of prototropy of bilirubin consistent with these observations are shown in schemes A and B.

Mesobilirubin, which lacks the vinyl groups necessary for such isomerisation but like bilirubin is capable of oxidation, was almost unchanged by treatment with sodium ethoxide. Thus, little of the verdinoid pigment obtained by heating bilirubin with sodium ethoxide is likely to have arisen by oxidation.

Prototropic changes of the sort outlined in schemes A and B are usually catalysed in

[6] Ref. 3, p. 123.
[7] Ref. 3, p. 126.
[8] Gray and Nicholson, *J.*, 1958, 3085.
[9] Gray and Nicholson, *Nature*, 1960, **185**, 380; Watson, Weimer, and Hawkinson, *J. Biol. Chem.*, 1960, **235**, 787.
[10] Gray, "The Bile Pigments," Methuen, London, 1953, pp. 1—10; Gray, Nicholson, and Nicolaus, *Nature*, 1958, **181**, 183.
[11] Ref. 2, p. 640.
[12] Fischer and Pleininger, *Z. physiol. Chem.*, 1942, **274**, 231.
[13] Siedel, *Z. physiol. Chem.*, 1935, **237**, 8.
[14] Fischer, *Z. Biol.*, 1915, **65**, 163.

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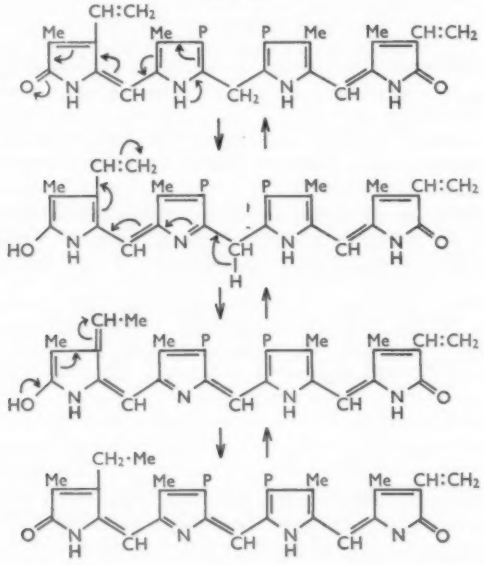
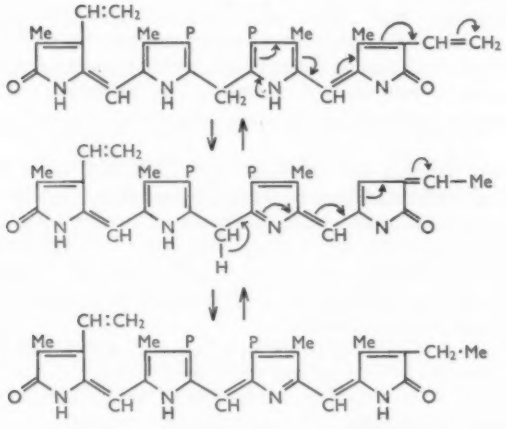
increasing order of efficiency by methoxide, ethoxide, isopropoxide and t-butoxide ions.[15] This order was observed (Table 1) when bilirubin was converted into verdinoid pigment by treatment with these alkoxides at room temperature. The effect of using solvents of various polarities could not be investigated owing to low solubility of bilirubin.

Scheme A



Scheme B



The spectroscopic properties of verdins, together with recorded values for glaucobilin, are shown in Table 2. The recorded data for biliverdin are summarised in Part II of the series.[1] There was no significant difference between the spectra of the verdinoid isomerisation product and the other verdins.

[15] Baker, "Tautomerism," Routledge, London, 1935.

The zinc complexes of the verdins had two main absorption maxima, at 695 (685 mμ according to Lemberg [16]) and 375—385 mμ, and a third small maximum at 270 mμ (see Fig. 1); there were differences in the ratio of the intensities of absorption at the two main maxima (Table 3). The ratio for the isomerisation product of bilirubin was similar to that of dihydrobiliverdin.

TABLE 1. *Influence of alkoxides on the isomerisation of bilirubin.*

Medium used	NaOH	NaOMe	NaOEt	NaOPr^i	KOBu^t
Yield (%) of verdinoid isomerisation product	—	4·6	5·7	8·5	11·3
Recovered bilirubin (%):					
(*a*) as rubin	3·2	2·3	2·0	1·5	1·4
(*b*) as verdin after atmospheric oxidation	75·1	73·0	70·1	65·2	66·1
Total (%) accounted for	78·3	79·9	77·8	75·2	78·9

TABLE 2. *Absorption maxima* (mμ) *of verdins.*

	In $CHCl_3$				In HCl–MeOH (5% w/v)			
Pigment	λ_1	λ_2	E_2/E_1 *		λ_1	λ_2	E_2/E_1	
Biliverdin (*a*)	640—645 (13·4)	377·5 (41·7)	3·10		670—680 (23·0)	377·5 (46·35)	2·02	
Verdinoid isomerisation product (*a*)	640—645	387	3·20		685	378	2·14	
Dihydrobiliverdin (*a*)	640—645	377	3·25		680	375	2·10	
Glaucobilin (*a*)	635—640 (13·5)	367·5 (43·12)	3·20		680—685 (24·5)	365 (45·8)	1·87	
Glaucobilin dimethyl ester (*b*)	Not given				670 (30·9)	Not given		
(*c*)	645 (17·0)							
(*d*)		363 (46·8) 309 (17·8)			Not given			
(*e*)		363 (46·7) 315 (24·6)			Not given			
(*f*)	636	367	1·79		647	367	1·54	

The millimolar extinction coefficients, when available, are shown in parentheses.

* Ratio of absorption at the two maxima calculated from reported data.

References: (*a*) Present preparation. (*b*) Lemberg, *Annalen*, 1932, **499**, 25. (*c*) Siedel, *Z. physiol. Chem.*, 1935, **237**, 8 (in benzene). (*d*) Pruckner and Stern, *Z. phys. Chem.*, 1937, *A*, **180**, 25 (in dioxan). (*e*) *Idem*, *ibid.*, 1939, *A*, **182**, 117 (in dioxan). (*f*) Goodwin and Srisukh, *Biochem. J.*, 1951, **48**, 199.

TABLE 3. *Absorption maxima* (mμ) *of zinc complexes of verdins in ethanolic zinc acetate.*

Pigment	λ_1	λ_2	E_2/E_1	Inflections
Biliverdin	695	385	1·91	640, 320, 270
Verdinoid isomerisation product	695	385	1·65	640, 330, 270
Dihydrobiliverdin	695	385	1·71	640, 330, 270
Glaucobilin (*a*)	695	380	1·41	
Glaucobilin (*b*)	695	380	1·40	
Glaucobilin XIIIα	695	375—380	1·39	
Lemberg's value for glaucobilin (*c*)	685			

References: (*a*) Prepared by ferric chloride oxidation of mesobilirubin. (*b*) Prepared by ferric chloride oxidation of mesobilirubinogen (following paper). (*c*) Lemberg, *Biochem. J.*, 1934, **28**, 978.

The zinc complexes are readily oxidised in solution to violinoid pigments, and this results in progressive changes of absorption spectra. All solutions of the complexes of pure verdins are green and do not fluoresce in ultraviolet light. Curve 1 in Fig. 2 shows the spectrum of a freshly prepared solution of the zinc complex of pure biliverdin. When this solution was kept, there was no change in its appearance but the absorption spectrum changed. The small maximum at 270 mμ increased, a maximum appeared at 310—320 mμ, the absorption at 430—510, 580—600, and 630—650 mμ increased, and the initial maximum at 695 mμ shifted gradually to lower wavelength; often another maximum at 650 mμ appeared. The solutions then exhibited orange fluorescence in ultraviolet light. Sometimes the maximum at 650 mμ did not appear but that at 695 mμ gradually shifted

[16] Lemberg, *Biochem. J.*, 1934, **28**, 978.

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towards 640 mμ. Orange fluorescence could not be detected while this maximum was above 660 mμ. Similar changes in the spectra and fluorescence were observed when the complexes were prepared from impure verdins containing traces of violinoid pigments.

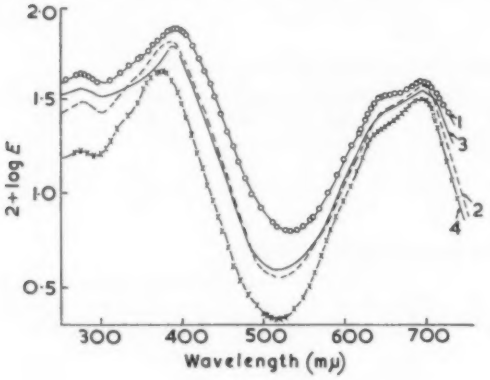

FIG. 1. *Absorption spectra of zinc complexes of verdins in ethanol*: **1**, *Biliverdin*; **2**, *dihydrobiliverdin*; **3**, *verdinoid isomerisation product*; **4**, *glaucobilin.*

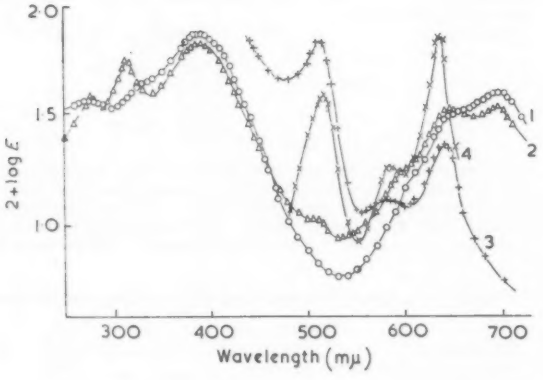

FIG. 2. *Absorption spectra of zinc complexes of pure and slightly oxidised biliverdin*: **1**, *Pure biliverdin*; **2**, *impure biliverdin*; **3**, *as* **1**, *after addition of iodine*; **4**, *as* **2**, *after addition of iodine.*

The zinc complexes of dihydrobiliverdin and of the verdin obtained by isomerisation were particularly susceptible towards oxidation in this way; that of glaucobilin was less readily oxidisable. The zinc complex of biliverdin itself was the most stable.

TABLE 4. *Absorption maxima* (mμ) *of zinc complexes of verdins after oxidation with iodine in ethanolic zinc acetate.*

Biliverdin	640—637·5	580	510—515
Verdinoid isomerisation product	632·5—635	580—585	515
Dihydrobiliverdin	632·5—635	580—585	515
Glaucobilin	630	585	515
Glaucobilin XIIIα	630—632·5	585	515

Optical densities of the maxima at 580—585 and 515 mμ increased, while that at 630—640 mμ decreased with time. The positions of the maxima at 580—585 and 510—515 mμ were not exactly reproducible and depended on concentration and time.

The zinc complexes of the different verdins could also be distinguished by determination of the red absorption maximum after oxidation of the complex with iodine (Table 4; Fig. 2, curve 3). Initially there was a red fluorescence in visible or ultraviolet light; this

rapidly changed through orange to lime-green, seen only in ultraviolet light. Such solutions had intense absorption peaks at about 635 mμ (stabilised by ammonia) and 515 mμ, with a subsidiary maximum at 580 mμ. The second of these maxima is due to choletelin formation; the others arise from violinoid pigments.

Similar maxima appeared on addition of iodine to aged solutions of zinc complexes of verdins (Fig. 2, curve 4), showing contamination by violinoid pigments.

The observations described are consistent with scheme A or B. The former would provide a verdin identical with that formally derived by ferric chloride oxidation of dihydrobilirubin. Dihydrobiliverdin thus obtained differs, however, from the verdinoid isomerisation product in the change of light absorption with pH.

Experimental

Ether was freed from peroxide by treatment with ferrous sulphate, and chloroform from acid by shaking it with potassium carbonate; the solvents were then distilled. The light petroleum used had b. p. 40—60°. Nitrogen was passed through alkaline sodium dithionite for the complete removal of oxygen.[17] Absorption spectra in the range 250—700 mμ were determined on the Hilger Uvispek Spectrophotometer of type H. 700, calibrated as recorded in Part II of this series.

Bilirubin.—The bilirubin used [ε = 55,600 at 450 mμ in chloroform; $\lambda_{max.}$ of iodine-oxidised zinc complex 639, 585, and 516 mμ (lit.,[18] 543 and 585 mμ] was purified as described in the preceding paper; special care was taken to ensure that the pigment was free from meso-impurities, which was demonstrated by oxidation as described below.

Dihydrobilirubin. Bilirubin (785 mg.; prepared from pig's bile) in 0·1N-sodium hydroxide (75 ml.) was treated with hydrogen in the presence of 10% palladium–charcoal (120 mg.) until absorption ceased. A further quantity of catalyst (120 mg.) was added and reduction was continued until 34·9 ml. of moist hydrogen at 21°/759 mm. had been absorbed. After acidification to Congo Red with 2·8N-hydrochloric acid, the product was separated by centrifugation and triturated with cold methanol. The catalyst was removed by dissolution of the pigment in boiling chloroform and filtration. Crystallisation from chloroform gave four crops. The two middle crops, united and recrystallised from chloroform (236 mg., 30%), had m. p. 310—315° (lit.,[19] m. p. 315°), ε 49,900 at 442 mμ in $CHCl_3$. The absorption maximum for the iodine-oxidised zinc complex in methanol was at 685, 586, and 515 mμ (lit.,[19] 639·5, 583·9 mμ).

Mesobilirubin. Bilirubin (0·5 g.) in 0·1N-sodium hydroxide (25 ml.) was shaken with hydrogen in the presence of 10% palladium–charcoal (1 g.) until the absorption ceased (3 hr.). After acidification with glacial acetic acid, the mixture was extracted with chloroform. The catalyst was separated and extracted with boiling chloroform. The united chloroform solution was green-yellow and gave no Ehrlich reaction; on evaporation it afforded a solid which crystallised poorly from chloroform. Sufficient chloroform (40 ml.) was added to redissolve the pigment which was then precipitated as a green-yellow mass by pouring the solution into stirred light petroleum. The crude substance was crystallised once from pyridine and then from glacial acetic acid, much verdinoid pigment remaining in the mother-liquors. The twice crystallised product was washed freely with alcohol for removal of further verdin and was recrystallised from chloroform, to give mesobilirubin (0·17 g., 34%), m. p. 315—320° (darkening from 250°) (lit.,[20] m. p. 315°), ε = 54,600 at 433—434 mμ in chloroform; $\lambda_{max.}$ of the iodine-oxidised zinc complex in methanol were at 626, 597, and 513 mμ (lit.,[19] 627·5, 576·2 mμ).

In a second preparation the yield was 58%.

Biliverdin, Dihydrobiliverdin, and Glaucobilin.—These were obtained by ferric chloride oxidation of the corresponding rubins in methanol. Because of the ease of further oxidation, conditions had to be strictly controlled. The method has been described in detail for biliverdin in Part II of the series.[1] All three pigments were obtained crystalline. Glaucobilin was also obtained by ferric chloride oxidation of mesobilirubinogen as described in the following paper.

[17] Linstead, Elvidge, and Whalley, "Modern Techniques of Organic Chemistry," Butterworths, London, 1955, p. 139.
[18] Ref. 2, Vol. II, p. 632.
[19] Ref. 2, Vol. II, p. 640.
[20] Ref. 3, p. 120, ref. 2, p. 650.

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Zinc Complexes of the Verdins.—These were prepared by dissolving the pure pigment in a saturated ethanolic solution of zinc acetate at room temperature. Light absorption was measured within 10 min. in a stoppered quartz cell (1 cm.). Two drops of 1% ethanolic iodine and one drop of concentrated aqueous ammonia were added to the solution in the cell; absorption was determined exactly 10 min. after addition of iodine (Fig. 2, curve 3). A second portion of the solution of zinc complex was left for 2 hr. and its absorption was again determined (Fig. 2, curve 2). Absorption of this solution was redetermined 10 min. after addition of the iodine solution and ammonia as before (Fig. 2, curve 4). Similar results were obtained with zinc complex solutions prepared from crude verdins known to be contaminated with violinoid pigments.

Oxidation of bile pigments by nitric acid. A suspension of the pigments (20 mg.) in water (1 ml.) was treated with concentrated nitric acid (2 ml.) and left for 48 hr. at 23° in the dark. Water (5 ml.) was added and the solution extracted with ethyl acetate (4 × 8 ml.). The extract was washed with water (3 × 5 ml.), and evaporated in a stream of air at 23°. The residue was dissolved in water (3 ml.), made alkaline (pH 8·5) by addition of sodium hydrogen carbonate, and extracted with chloroform (4 × 8 ml.). These extracts were washed as before, dried by filtration, and evaporated at room temperature, affording a neutral fraction (A). The alkaline aqueous residue was acidified with 11N-hydrochloric acid and again extracted with chloroform, and the extract was washed and dried. Evaporation afforded an acid fraction (B).

For identification of the products paper chromatography with descending development on Whatman No. 2 paper with 16 : 3 : 1 ethanol–water–ammonia (*d* 0·88) was used. The products (0·01 mg.) were applied to the paper in methanol. The developed chromatogram was momentarily immersed in 1 : 1 acetone–ethanol, blotted, and immersed in a tank containing chlorine. After removal of chlorine by aeration and immersion of the paper in a saturated solution of *o*-tolidine in 2N-acetic acid to which an equal volume of 0·05N-potassium iodide had been added, the imides appeared as blue spots.[21] Authentic hæmatinimide and ethylmethylmaleinimide were used as markers; they had R_F 0·56 and 0·83 respectively.

Hæmatinimide was found in all the acid fractions (B). The neutral fractions (A) from the verdinoid isomerisation product, dihydrobiliverdin, mesobiliverdin, crude commercial bilirubin, dihydrobilirubin, and d-urobilin contained ethylmethylmaleinimide; fractions (A) from biliverdin, bilirubin from pig's bile, and purified commercial bilirubin did not contain this imide.

Oxidation of the verdinoid isomerisation product on a larger scale (50 mg.) gave crystalline ethylmethylmaleinimide, m. p. 68° (lit.,[22] m. p. 68°), from the neutral fraction.

Isomerisation of Bilirubin to Verdin by Treatment with Sodium Ethoxide in Absence of Air.—Through a solution of pure bilirubin (50 mg.) in ethanol (10 ml.) nitrogen was passed for 10 min. to expel air. 1·22N-Sodium ethoxide (10 ml.) was then introduced and the mixture was boiled under reflux in the oxygen-free atmosphere. After about 3 hr. the orange-brown colour of bilirubin had changed to olive-green and later to deep green. The cooled mixture was diluted with water (75 ml.), acidified with glacial acetic acid (10 ml.), and shaken with ether (250 ml.). The ethereal layer was exhaustively extracted with N- and then 2·8N-hydrochloric acid; the two acid fractions had absorption maxima at 340—360, 650—680 mμ (the exact position depended on the concentration of the pigment), and 385, 660 mμ, respectively. The acid fractions were separately extracted with chloroform. All these operations were performed under nitrogen. The extracts were washed with water (4 × 20 ml.), dried by filtration, and evaporated to dryness *in vacuo*. The two fractions were chromatographed separately on magnesia. Biliverdin was first eluted with 1 : 1 light petroleum–chloroform, leaving a small amount of residual bilirubin on the column which was later eluted with chloroform. The yields of verdin were determined spectroscopically both in chloroform and in 5% w/v methanolic hydrogen chloride, molecular extinction coefficients being assumed as for biliverdin (Table 2). The results calculated from the two maxima in the two solvents were almost identical and an average value of these was taken. The ethereal layer was washed with water, dried by filtration, and evaporated *in vacuo*. The residue, dissolved in chloroform, was united with the bilirubin fractions eluted from the columns and was immediately analysed for residual bilirubin. The results of a series of these experiments in which bilirubin was refluxed for variable times are tabulated.

[21] Ref. 17, p. 11.
[22] Muir and Neuberger, *Biochem. J.*, 1949, **45**, 164.

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Refluxing (hr.)	Verdinoid isomerisation product (%)			Residual bilirubin (%)	Pigment accounted for (%)
	in N-acid	in 2·8N-acid	Total		
0·0	0	0	0	96	96
0·5	—	14	14	86	100
1·0	26	4	30	64	94
6·0	53	—	—	29	
8·0	67	8·6	76	16	92
8·0	69	4	73	14	87

If contact with air is not restricted to a minimum and the extraction is not performed rapidly, then the amount of pigment which requires extraction with 2·8N-acid increases and the total amount of verdin is considerably reduced.

Comparative Behaviour of Bilirubin and Mesobilirubin towards Sodium Ethoxide.—Bilirubin (58 mg.) and mesobilirubin (60 mg.) were separately treated, as described above, for 8 hr. with 1·22N-sodium ethoxide, the yields of verdinoid products being 75% and 7% respectively. No visible verdin was formed from bilirubin or mesobilirubin on similar treatment with methanol alone; however, extraction of these solutions by the procedure outlined above resulted in isolation of some verdin, undoubtedly arising by oxidation; the yield was greater in the case of mesobilirubin than of bilirubin.

Effect of Alkoxides on the Isomerisation of Bilirbin.—A standard solution of bilirubin in chloroform (0·0698 g./100 ml.) was prepared; 3 ml. portions were measured into five similar tubes and evaporated almost to dryness *in vacuo*. Approximately 3% solutions of sodium methoxide, sodium ethoxide, sodium isopropoxide, and potassium t-butoxide were prepared in corresponding alcohols and, together with aqueous 3% sodium hydroxide, were titrated against standard hydrochloric acid. An amount of each, equivalent to 2 ml. of 1·22N-solution/10 mg. of bilirubin, was added to each tube and the solutions were made up to 15 ml. with the appropriate alcohol. The solutions were stored under nitrogen in the dark at room temperature. After 6 days the solutions were diluted with water (10 ml.), the excesses of alkoxide were neutralised by glacial acetic acid (2 ml.), and the pigments were extracted into peroxide-free ether (40 ml.). The ether solutions were washed with water (10 ml.) and extracted with 2·8N-hydrochloric acid (14 ml.). Pigment in the acid extract was taken into chloroform, washed with water, dried by filtration, and diluted to 20 ml., and its verdinoid content was determined spectroscopically, ε values being assumed to be those of biliverdin. The acid-extracted ether containing residual bilirubin was washed with water, dried by filtration, and evaporated *in vacuo*; the residue was dissolved in chloroform (20 ml.). This residual bilirubin was estimated spectrophotometrically 1 hr. after dissolution of the ether residue and when most of the bilirubin had been oxidised by atmospheric air to biliverdin. Remaining bilirubin was estimated by spectrophotometry at 450 mμ, and the resulting biliverdin at 375 mμ. The results are recorded in Table 1.

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THE DEPARTMENT OF CHEMICAL PATHOLOGY, KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, LONDON, S.E.5. [*Received, October 20th*, 1960.]

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442. *The Chemistry of the Bile Pigments. Part IV.*[1] *Spectrophotometric Titration of the Bile Pigments.*

By C. H. Gray, A. Kulczycka, and D. C. Nicholson.

Spectrophotometric titration curves of four main types of bile pigments and related dipyrryl compounds reveal a predominantly basic character in urobilins, violins, and verdins, the basic strengths decreasing in that order, and a predominantly acidic character in rubins. Implication of these results on the structure of the pigments is discussed.

All naturally occurring bile pigments contain carboxyl groups, separated from the main chromophores by two methylene groups, so that their ionisation is not detectable spectrophotometrically. Thus, the spectra of esters of verdins and of carboxyethylporphyrins are identical with those of the corresponding free pigments.[2,3] Changes in the spectra of bile pigments accompanying change of pH, therefore, arise from addition of protons to, or their removal from, the main chromophores of these compounds.

We have studied rubins, urobilins, verdins, and violins as well as simple dipyrrylmethenes representative of the chromophores of the first two classes of these pigments. We first used McIlwain's buffer solutions,[4] but these are not of constant ionic strength, as shown by an approximately six-fold change of conductivity over their entire range. Their pH range was unsatisfactory for the spectrophotometric study of the urobilins and, less so, of the rubins, which were, therefore, also examined in veronal–acetate buffers which are of constant ionic strength ($\mu = 0{\cdot}1$).[5] These buffers were, however, unsuitable for the investigation of the verdins, but were employed for mesobiliviolin. Results with the two buffer systems were nevertheless almost identical.

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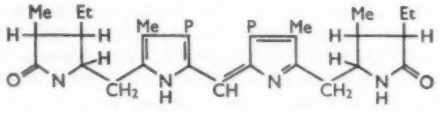

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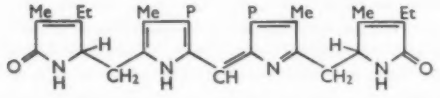

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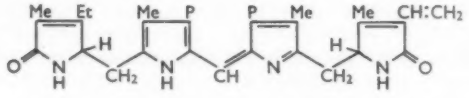
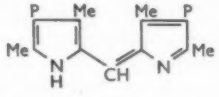


(IV)



The Urobilins.—The urobilins are orange in aqueous acid solution; in neutral or alkaline solution they are yellow. Stercobilin (I), i-urobilin (II), d-urobilin (III *), and the dipyrrylmethene (IV) gave similar spectroscopic absorption curves, all of which varied

* For an alternative formula see ref. 6.

[1] Part III, preceding paper.
[2] Lemberg and Legge, "Haematin Compounds and Bile Pigments," Interscience Publ. Inc., New York, 1949, p. 75.
[3] Holt and Jacobs, *Ann. J. Bot.*, 1954, **41**, 710.
[4] "Handbook of Chemistry and Physics," Chemical Rubber Publ. Co., 1950, p. 1487.
[5] Neuberger and Scott, *Proc. Roy. Soc.*, 1952, *A*, **213**, 307.
[6] Siedel and Meier, *Z. physiol. Chem.*, 1936, **242**, 101.

Spectrophotometric titration data for the urobilins in veronal–acetate buffers.

Pigment	Maximum in acid (mμ)	pH	Maximum in alkali (mμ)	pH	p*K*	Posn. (mμ) of isosbestic point
Dipyrrylmethene (IV) ...	480	6·80	455—460	9·75	8·50	450
Stercobilin (I)	490	6·15	452·5—455	8·70	7·60	458
i-Urobilin (II)	491	5·90	455—460	8·60	7·40	460
d-Urobilin (III)	491—492	5·75	460	8·40	7·20	460

in the same way with pH. The spectral absorption curves of stercobilin shown in Fig. 1 are typical.

Differences in the spectroscopic behaviour between the free forms and the hydrochlorides of urobilins and allied dipyrrylmethenes have been reported by Pruckner and

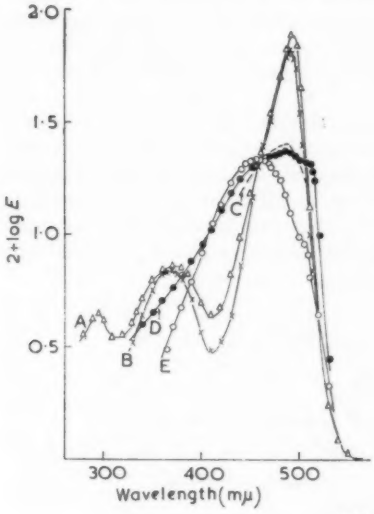


FIG. 1. *Spectrophotometric absorption curves of stercobilin* (I) *in veronal–acetate buffers*: A, pH 1·0 (*without buffer*); B, pH 7·0; C, pH 8·4; D, pH 9·1; E, pH 12·0 (*without buffer*).

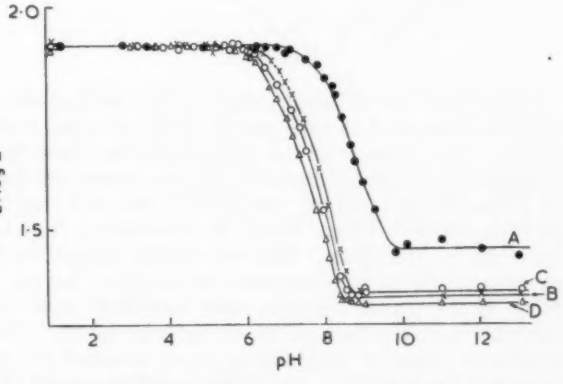


FIG. 2. *Spectrophotometric titration curves of urobilins in veronal–acetate buffers*: A, *dipyrrylmethene* (IV); B, *stercobilin* (I); C, *i-urobilin* (II); D, *d-urobilin* (III). *Low and intermediate* pH *plots refer to an absorption maximum at* ca. 490 mμ; *high* pH *plots refer to an absorption maximum at* ca. 460 mμ.

Stern.[7] The free compounds in dioxan gave absorption curves resembling those found by us for solutions of high pH; hydrochlorides in the same solvent gave curves resembling those shown here for solutions of low pH. The spectrophotometric titration curves and the corresponding data for the pigments in the veronal–acetate buffers are shown in Fig. 2 and in the Table respectively. The absorption curves at pH above 9 had additional

[7] Pruckner and Stern, *Z. phys. Chem.*, 1937, *A*, **180**, 25; 1938, *A*, **182**, 117.

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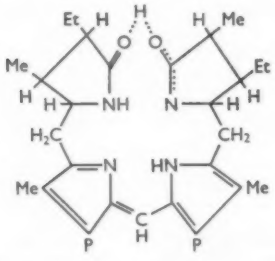
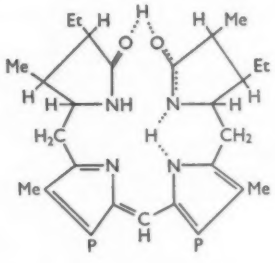
maxima at about 510 mμ; they did not then pass through the isosbestic point owing to complex formation, especially with i-urobilin at pH 12—13. The titration curves in McIlwains buffers can only be determined with accuracy on the acid side of the pK, which was only about 0·1 of a pH unit higher than that in the veronal–acetate buffer. The isosbestic points and the molecular extinction coefficient in acid and alkaline solution were also the same for the two buffers.

The dipyrrylmethene group present in the urobilins contains one nucleophilic pyrroline-nitrogen atom; these compounds, therefore, have a predominantly basic chromophore. The titration curves of the urobilins show that these pigments may be arranged in the decreasing order of their basic strength: stercobilin, i-urobilin, and d-urobilin, the conjugate acids having pK 7·60, 7·40, and 7·20 respectively. The stronger basic character of stercobilin must be attributed to the saturated nature of the terminal rings. In stercobilin the electron density about the pyrroline-nitrogen atom of the dipyrrylmethene chromophore, being undisturbed by effects from remote parts of the molecule, may be assumed more suitable for external co-ordination (*e.g.*, of a proton) than it is around the nitrogen in the other molecules.

Recently, Lemberg has suggested a monolactam structure for stercobilin, with a hydrogen bonding between the two terminal oxygen atoms (V). Such a structure, unlike the bislactam form, provides two replaceable *N*-hydrogen atoms and two electron-donating nitrogen atoms, thus accounting for the inclusion of one metal atom in each molecule of metal complex.[8] In one end ring of stercobilin there is thus a nucleophilic nitrogen atom which might co-ordinate to itself the proton formulated as part of the dipyrrylmethene unit. A further hydrogen-bonded structure would arise as shown in (VI).

(V)





(VI)

Stercobilin has no unsaturation in the end ring to restrain by mesomeric effects the electrons presumed to take part in such hydrogen bonding which would, therefore, be strong. The electrons of the dipyrrylmethene group thus partially relieved of their rôle in binding the hydrogen atom of the pyrrole group, will have a greater ability to co-ordinate an extramolecular proton. In i-urobilin, the end rings are unsaturated and the electrons of their nitrogen atoms being, in consequence, less localised than the corresponding electrons in stercobilin, will less readily engage in hydrogen-bond formation. The electrons of the dipyrrylmethene chromophore, having, therefore, to bind the hydrogen atom on the pyrrole nitrogen more completely than in stercobilin, will be less readily available for co-ordination of an external proton. In d-urobilin, the presence of an additional centre of unsaturation in, or attached to, one end ring, enhances the effect described for i-urobilin; the dipyrrylmethene group of this pigment should, therefore, even less readily co-ordinate to itself an external proton. Thus, the decrease in nucleophilic properties of the urobilins, in order stercobilin, i-urobilin, and d-urobilin, is understood.

The dipyrrylmethene (IV), the conjugate acid of which dissociates with pK 8·50, is

[8] Lemberg, personal communication.

an even stronger base than stercobilin; the greater availability of electrons in this compound may be readily explained by a positive inductive or hyperconjugative effect from the α-methyl groups.

Confirmation that the pyrroline-nitrogen atom is the spectroscopically active nucleophilic centre of the urobilins was sought by the examination of stercobilinogen, the dihydro-derivative of stercobilin, which contains no pyrroline-nitrogen atom. The compound, however, was too labile for determination of its pure spectrum, being rapidly autoxidised to stercobilin. The dipyrrylmethane obtained by reduction of compound (IV) with sodium amalgam was also unstable and could not be studied in buffer solutions owing to powerful absorption of the latter in the ultraviolet region. It was, nevertheless,

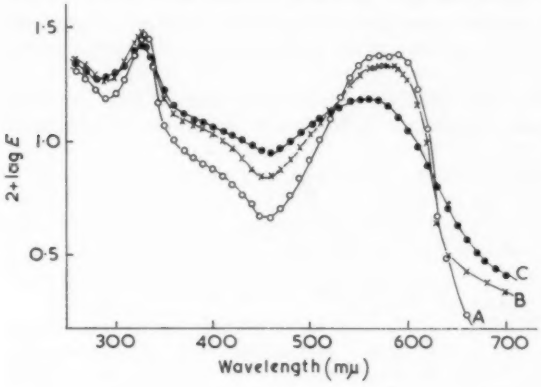


FIG. 3. *Spectrophotometric absorption curves for mesobiliviolin* (VII) *in McIlwain buffers*: A, pH 1 (*without buffer*); B, pH 2·2; C, pH 4·4.

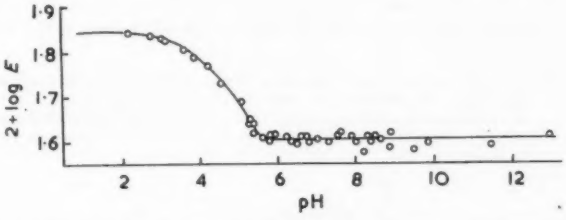
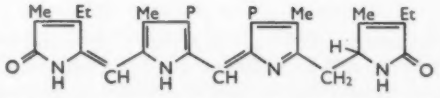


FIG. 4. *Spectrophotometric titration curve for the* 550—585 mμ *absorption maximum of mesobiliviolin* (VII) *in veronal–acetate buffer.*

clearly established that this substance, which also contains no pyrroline-nitrogen atom, in absence of buffer absorbs more strongly, at its maximum (268 mμ) in alkaline than in acid solution and, therefore, resembles a rubin (see below).

Violins.—Aqueous solutions of mesobiliviolin are red-violet at pH values above 5 and blue-violet or blue at pH values below 4. Absorption curves for mesobiliviolin (VII) in McIlwain's buffers are shown in Fig. 3. As with urobilins, but less readily so, alkaline solutions of mesobiliviolin rapidly form metal complexes, the solutions in consequence developing red fluorescence.

Fig. 4 shows the spectrophotometric titration curve obtained for the 550—585 mμ absorption maximum of mesobiliviolin in veronal–acetate buffer; points below pH 3 were



(VII)

obtained in hydrochloric acid, the solution then being of different ionic strength. In veronal–acetate buffer full titration curves were obtained for only a few pH values and these were identical with those obtained for solutions in McIlwain buffers (Fig. 3).

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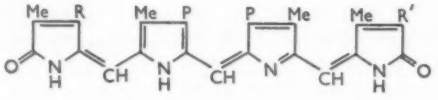
As with urobilins and consistent with the presence of a pyrroline-nitrogen atom, mesobiliviolin shows an overall decrease of maximal optical absorption with increase of pH; in strongly acid solution, absorption is particularly enhanced. The chromophore of this pigment is therefore basic, the conjugate acid dissociating with pK about 4·0. Free mesobiliviolin is, then, a weaker base than any of the urobilins. This is expected, since in this pigment electrons of the nucleophilic nitrogen atom are in a more extensive chromophore (three conjugated rings instead of two, as in urobilins), and are, therefore, less readily available for external co-ordination of a proton. The chromophore also differs from that of the urobilins in that it contains an electronegative carbonyl group. The effect of this is considered below.

Verdins.—Aqueous solutions of biliverdin and dihydrobiliverdin are green-blue and those of glaucobilin are blue. The solutions are almost the same colour whether acidic or alkaline. Spectroscopic data and absorption curves for the verdins are given in the preceding paper.

Of the verdinoid pigments, glaucobilin (VIIIa), dihydrobiliverdin (VIIIb), and biliverdin (VIIIc) were examined. These compounds in McIlwain's buffers show inflections

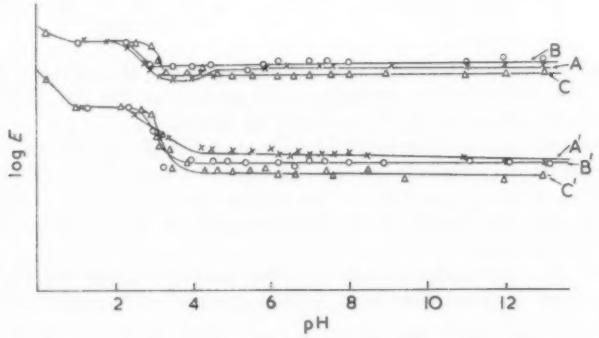


(VIIIa) R = R′ = Et (VIIIb) R = CH:CH$_2$; R′ = Et

(VIIIc) R = R′ = CH:CH$_2$ or R = Et; R′ = CH:CH$_2$

of their spectrophotometric titration curves at pH values below 4 (Fig. 5); no attempt was, therefore, made to reproduce these curves in veronal–acetate buffers. The verdins, especially glaucobilin, were unstable at pH between 2·5 and 5, absorption at both maxima

FIG. 5. *Spectrophotometric titration curves of verdins in McIlwain buffers*: A, *biliverdin* (VIIIc) (~360 mμ max.); B, *dihydrobiliverdin* (VIIIb) (~360 mμ max.); C, *mesobiliverdin* (VIIIa) (~360 mμ max.); A′, *biliverdin* (~660 mμ max.); B′, *dihydrobilirubin* (~660 mμ max.); C′, *mesobiliverdin* (~660 mμ max.). *Positions of curves have been adjusted for convenience of illustration; no scale for the ordinate is therefore given.*



rapidly decreasing. The maximum at 660 mμ was replaced by a new one at 540—580 mμ, and increased absorption between 350 and 250 mμ accompanied the disappearance of the maximum at 365 mμ. These changes, in the case of glaucobilin and especially at pH 3·4, are accompanied by development of a violet colour and indicate conversion into a purpurin. Because of this instability, titration curves for verdins derived from complete absorption curves show a minimum between pH 2·5 and 5. More accurate curves for these pigments

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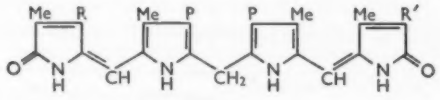
were, therefore, obtained by determining the optical density first at the lower, less stable, maximum within one minute of preparation of the solutions. Curves so obtained are given in Fig. 5.

Verdins, like violins and urobilins, provide titration curves showing greater maximal absorption at low pH than at high pH. Instability of the verdins at low pH precludes the derivation of an exact pK value for the conjugate acids of these pigments, an approximate value being 3. Nevertheless, titration curves for the verdins are without inflections over the range of pH where these are found for violins and urobilins. The verdins are, therefore, much weaker bases than violins or urobilins and this is expected, since the electrons of their pyrroline-nitrogen atoms, being included in the most extensive resonating system found in the bile pigments, are the least readily available for the co-ordination of an external proton. For the same reason, the pK of biliverdin is lower than that of dihydrobiliverdin or glaucobilin.

Both verdins and violins contain electronegative carbonyl groups in their chromophores; these must also be partly responsible for the lower basic strength of these pigments than of the urobilins. Complexity of the chromophores of the basic bile pigments increases from urobilins (two conjugated pyrrole rings), through violins (three conjugated rings with one carbonyl group), to verdins (four conjugated rings with two carbonyl groups). Attachment of protons to these chromophores would be expected to disturb the electronic structures of the urobilins most, of the violins moderately, and of the verdins least. It is significant that the ratios of optical absorption of the protonated molecule to that of the unprotonated molecule decrease in this order.

Rubins.—Aqueous solutions of rubins are yellow, whether they are acid or alkaline, having one broad maximum in the blue, the wavelength of which decreases in the order bilirubin (IXa), dihydrobilirubin (IXb), dimesobilirubin (IXc).[1] Absorption spectra of



(IXa) R = R′ = CH:CH$_2$

(IXb) R = CH:CH$_2$, R′ = Et or *vice-versa*

(IXc) R = R′ = Et

these compounds are similar; those for mesobilirubin at various pH values in McIlwain's buffers are typical and are presented in Fig. 6, because this pigment contains the same β-substituents as i-urobilin, mesobiliviolin, and glaucobilin. The titration curves for the rubins and the analogous dipyrrylmethenes (X), (XI) are shown in Fig. 7, for solutions in McIlwain's buffers. Because of the instability of rubins toward light and air, these curves were constructed by measuring absorption rapidly, first at the maximum and immediately afterwards in the region of the isosbestic point, always within 3 min. of preparation of solution. In contrast to these results, Williams and Ruz, and Martin,[9] found a decrease of optical density with increasing pH for solutions of bilirubin but describe no precautions against the instability of their stock solution of pigment. At pH's below 5, the solutions sometimes developed turbidity, it then being difficult to obtain reproducible optical densities. Absorption curves of these solutions, especially those of bilirubin (the least soluble), did not always pass through the isosbestic point. For bilirubin, an anomalous minimum, which disappeared with time, appeared in the titration curve.

Rubins form no metal complexes;[10] they therefore cannot contain nucleophilic nitrogen

[9] Williams and Ruz, *Rev. Soc. Argentina de Biol.*, 1943, **19**, 401; Martin, *J. Amer. Chem. Soc.*, 1949, **41**, 1230.

[10] Ref. 2, pp. 108, 123.

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atoms. They thus lack the basic character of urobilins, violins, and verdins; and, of all the bile pigments, they alone do not form hydrochlorides. The classical structure for bilirubin with hydroxyl groups in the end α-positions contains one formally nucleophilic nitrogen atom in each end ring; the bislactam form (IXa) contains no nucleophilic nitrogen

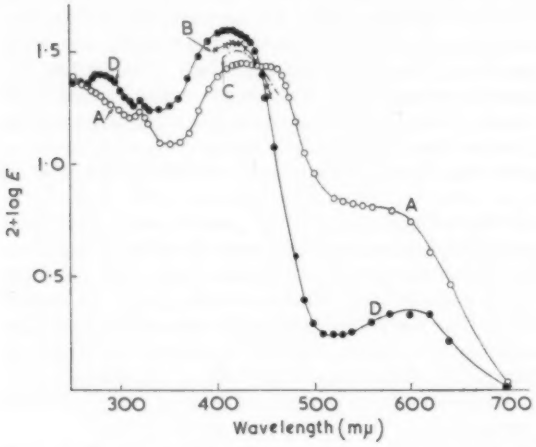
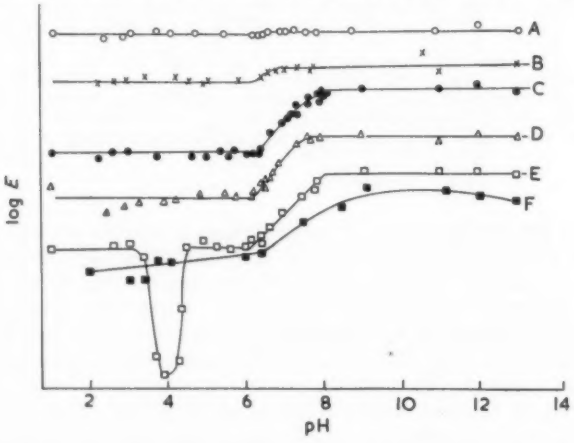


FIG. 6. *Spectrophotometric absorption curves of mesobilirubin* (IXc) *in McIlwain's buffers*: A, pH 1 (*without buffer*); B, pH 7; C, pH 7·8; D, pH 13 (*without buffer*).

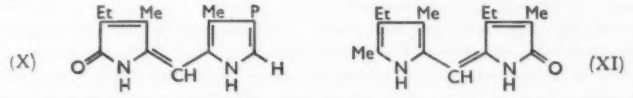
FIG. 7. *Spectrophotometric titration curves of rubins and allied dipyrrylmethenes in McIlwain buffers*: A, *the dipyrrylmethene* (X); B, *the dipyrrylmethene* (XI); C, *mesobilirubin* (IXc); D, *dihydrobilirubin* (IXb); E, *bilirubin* (IXa); F, *readings obtained for bilirubin solution after* 1 *hr. Positions of curves have been adjusted for convenience of illustration; no scale for the ordinate is therefore given.*



atoms and is, therefore, more compatible with the above facts. The dipyrrylmethene units in bilirubin each contain a carbonyl group capable of accommodating the anionic charge resulting from the dissociation of an NH group, and the rubins should, therefore, be well stabilised in the anionic form. All four *N*-hydrogen atoms in the bislactam structure should, therefore, individually be more easily ionised than the corresponding acidic hydrogen atom in pyrrole itself. A predominantly acidic character for these pigments is also consistent with the prototropy occurring in bilirubin as described in the preceding paper, because these two properties often co-exist.[11] The increased absorption of solutions

[11] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell, London, 1953, pp. 543—550.

of high pH, therefore, probably corresponds to the separation of a proton from a molecule of the free rubin. The titration curves show that bilirubin, dihydrobilirubin, and mesobilirubin have pK about 7·1, 7·2, and 7·3, respectively. Because, however, of the instability of the rubins, their irregular behaviour below pH 5, and the small increments of optical density with pH, these values are not accurate. Nevertheless, both in McIlwain's buffer and veronal–acetate buffer, the same pattern of absorption was always observed. The apparent increase of acid strength in the order mesobilirubin, dihydrobilirubin, bilirubin is consistent with the same order for increasing unsaturation and tolerance of anionic change.



Isoneoxanthobilirubic acid (X) and 3,4′-diethyl-5-hydroxy-4,3′,5′-trimethyldipyrryl methene (XI) resemble the hydroxydipyrrylmethene units of rubins. Both give yellow aqueous solutions, the colour being the same in acid and alkali; the titration curves are given in Fig. 7. Isoneoxanthobilirubic acid in all aqueous solutions has an absorption maximum at 395—400 mμ, the optical density being almost independent of pH (Fig. 7). The dipyrrylmethene (XI) had an absorption maximum at 395—410 mμ in acid buffers and at 375—397 mμ in alkaline buffers, with one isosbestic point at 420 mμ. There is little indication of acidity in these compounds; like the rubins, however, they do not form metal complexes or hydrochlorides and cannot contain electron-donating nitrogen atoms. They are accordingly better represented by the lactam formulæ shown than as hydroxypyrroles.[12]

Experimental

Stercobilin and d-Urobilin.—Stercobilin hydrochloride, $[\alpha]_D$ −3700° in $CHCl_3$, and d-urobilin hydrochloride, $[\alpha]_D$ +5000 in $CHCl_3$, were isolated as previously described [13] and were recrystallised from chloroform. $10^{-3}\varepsilon = 92{\cdot}9$ at 496 mμ for stercobilin in $CHCl_3$, and 93·7 at 499 mμ for d-urobilin in $CHCl_3$.

i-Urobilin.—i-Urobilin was prepared from bilirubin by reduction to mesobilirubinogen with sodium amalgam, followed by oxidation in glacial acetic acid.[6] Final recrystallisation of the hydrochloride from chloroform containing a little dry acetone afforded a product with $\lambda_{max.}$ (in $CHCl_3$) 499 mμ (ε $7{\cdot}21 \times 10^{-4}$).

Mesobiliviolin.—Mesobilirubinogen, prepared as above from bilirubin (100 mg.), was dissolved in methanol (10 ml.). 20% Ferric chloride in concentrated hydrochloric acid (1 ml.) was added and the solution was boiled under reflux for 15 min. After addition of water (30 ml.), pigments were re-extracted into ether (final volume, 300 ml.). Urobilin was removed by washing the ethereal extract with water until no further yellow colour appeared in the washings. The washed ethereal solution was exhaustively extracted with 2·8N-hydrochloric acid, and violet pigment was then extracted from the acid extract into chloroform (final volume, 80 c.c.). The chloroform solution was washed free from acid, filtered through chloroform-impregnated paper, and evaporated to dryness. The dry residue of violinoid pigment, dissolved in the smallest possible quantity of 2 : 1 chloroform–ether, was brought on to a column of magnesium oxide (35 × 1 cm.). Elution with the same solvent caused separation of the pigment into an immobile fraction of indefinite purple colour and a mobile band. Further development resolved the mobile band into (*a*) a small upper verdinoid band, (*b*) an intermediate violet band (main fraction), and (*c*) a lower red band (smallest). Band (*b*) was composed of pure violin which had $10^{-3}\varepsilon = 20{\cdot}0$ at 565 mμ and 21·6 at 327·5 mμ in 5% w/v HCl–MeOH, 12·0 at 565 mμ and 18·5 at 327 mμ in $CHCl_3$, and 23·8 at 602·5 mμ and 22·3 at 327·5 mμ in $CHCl_3$ shaken with 2·8N-HCl. The zinc complex in ethanol was blue with bright red fluorescence and had $\lambda_{max.}$ at 632·5, 582·5, and 340 mμ (lit.,[14] 630·6, 580—566 mμ in EtOH).

[12] Fischer and Orth, "Die Chemie des Pyrrols," Academische Verlagsges., Leipzig, 1937, Vol. II, p. 649.
[13] Gray and Nicholson, *J.*, 1958, 3085.
[14] Siedel, *Z. physiol. Chem.*, 1935, **237**, 8.

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In this preparation, a larger quantity of ferric chloride, prolonged heating, or too long contact with air, results in formation of purpurinoid pigments, the visible absorption maxima of which are shifted by about 10 mμ towards lower wavelength. These are readily distinguished from true violin by their failure to undergo oxidation to verdin on further treatment with ferric chloride.

Dihydrobilirubin and Mesobilirubin.—These were obtained by quantitative hydrogenation of bilirubin at atmospheric pressure.

Biliverdin, Dihydrobiliverdin, and Mesobiliverdin (Glaucobilin).—These were prepared by oxidation of bilirubin, dihydrobilirubin, and mesobilirubin (see below), respectively, with ferric chloride. Methods used for the production of these pigments and their spectroscopic characteristics are described in the preceding paper.

Glaucobilin.—Glaucobilin was also obtained by oxidation of mesobilirubinogen. The mesobilirubinogen prepared by reduction of bilirubin (200 mg.) with 2·5% sodium amalgam (2 × 10 g.), as mentioned in the description of i-urobilin, was boiled under reflux in methanol (10 ml.) and 20% ferric chloride solution (1 ml.) for 45 min. Pigments were brought into chloroform solution by the procedure described for mesobiliviolin, and the washed solution was dried by filtration. Initial chromatography on magnesium oxide separated an immobile band (*a*) and a mobile band (*b*). Elution with 2 : 1 chloroform–ether caused slight development of band (*a*) into 5 fractions (violet, yellow, violet, green-yellow, and pink) of increasing mobility. Band (*b*) separated into a red-violet (minor and more mobile) and a blue fraction (major and less mobile). The pigment of the blue band in chloroform had maxima at 635—640 and 370 mμ and was united with the verdinoid band obtained in the preparation of mesobiliviolin. These combined fractions (3·87 mg.) were rechromatographed and found to be homogeneous. The spectral characteristics are given in the preceding paper.

3,4′-Diethyl-5-hydroxy-4,3′,5′-trimethyldipyrrylmethene (XI).—Ethyl hydroxyiminoacetate was prepared and purified by Corwin and Ellingstone's method.[15] It did not crystallise. Distillation afforded a slightly yellow, odourless product, b. p. 151—152°/24 mm., in 47% yield.

Ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate, m. p. 148°, was prepared by the Knorr condensation of the oxime-ester and acetylacetone in 55% yield (lit.,[16] m. p. 143°, yield, crude, 55%).

Ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate, m. p. 94°, was prepared [17] from the acetyl derivative in quantitative yield by hydrogenation at high temperature and pressure.

3-Ethyl-2,4-dimethylpyrrole (cryptopyrrole).—The last-mentioned ester (33 g.) and potassium hydroxide (20 g.) in water (100 ml.) were boiled for 3 days under nitrogen. The solution was saturated with sodium chloride and extracted with ether (10 times). The extracts were dried (K_2CO_3), the solvent was removed, and the residue distilled, to give the pyrrole, b. p. 90°/14 mm. (18 g., 82%). Fischer and Orth [18] obtained the pyrrole in an overall yield of 62% by one-step reduction of the 3-acetyl group and decarboxylation with hydrazine hydrate in alcoholic sodium ethoxide. The recorded method [19] of bromination gave 5-bromo-3,4′-diethyl-4,3′,5′-trimethyldipyrrylmethene hydrobromide, m. p. 148°, and thence by potassium acetate in boiling acetic acid,[20] 3,4-diethyl-5-hydroxy-4,3′,5′-trimethyldipyrrylmethene, m. p. 245—248°.

The corresponding methane was obtained by reduction of this compound in methanol with sodium amalgam.

Diethyl 3,3′,5,5′-Tetramethyldipyrrylmethene-4,4′-dicarboxylate (IV).—Diethyl hydroxyiminomalonate, prepared by Cherchez's method,[21] had b. p. 175—185°/15 mm. (yield 75%) (lit.,: yield 80—90%, b. p. 172°/12 mm.).

Thence the method of Gresham *et al.*[22] gave 4-acetyl-5-oxohexanoic acid, b. p. 150—170°/1·5 mm. (36%) (lit.: 124—142°/1 mm., 42%), m. p. 76—80° (from hexane; 15%).

To a stirred solution of this acid (86 g., 1·5 mol.) in glacial acetic acid (260 ml.) containing anhydrous sodium acetate (130 g.) and zinc dust (111 g.), was added diethyl hydroxyiminomalonate (94·7 g., 1·47 mol.) in acetic acid (120 ml.) and water (50 ml.) at a rate to maintain

[15] Corwin and Ellingstone, *J. Amer. Chem. Soc.*, 1944, **66**, 1150.
[16] Ref. 12, Vol. I, p. 193.
[17] Eisner, Lichtarowicz, and Linstead, *J.*, 1957, 733.
[18] Ref. 12, Vol. I, p. 54.
[19] Ref. 12, Vol. I, p. 73.
[20] Ref. 12, Vol. II, p. 114.
[21] Cherchez, *Bull. Soc. chim. France*, 1930, **47**, 1279.
[22] Gresham, Jansen, Shaver, and Bears, *J. Amer. Chem. Soc.*, 1951, **73**, 2345.

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refluxing. Then the mixture was boiled for a further 2 hr. and poured on ice (2 kg.). After storage in a refrigerator overnight, the crystalline 4-ethyl hydrogen 2,5-dimethylpyrrole-2,4-dicarboxylate was filtered off and dried. It (80 g., 67%) had m. p. 158—160°, unchanged by recrystallisation (lit.:[23] 59%, m. p. indefinite; after several crystallisations from benzene, m. p. 154—156°).

This product gave the orange hydrochloride, m. p. 238°, of ester (IV) in 70% yield by Fischer and Morgenroth's method.[24]

The corresponding dipyrrylmethane was obtained by reduction of the methene in methanol with sodium amalgam.

Isoneoxanthobilirubic Acid (X).—A mixture of neoxanthobilirubic and isoneoxanthobilirubic acid obtained from mesobilirubin (2·07 g.) by fusion with resorcinol (60 g.), according to the method of Fischer and Hess,[25] was esterified by hydrogen chloride in methanol. Fractional crystallisation from ethanol–methanol afforded the iso-ester (190 mg.), m. p. 200° (lit.,[26] 203°). The free acid (X) (15 mg.), obtained by hydrolysis of the ester, crystallised from methanol–acetic acid, had m. p. 232° (lit., 240—242°).

Determination of Spectrophotometric Titration Curves.—A Hilger H 700 spectrophotometer with a quartz prism was used. Wavelength setting and optical density readings were checked with calibrated didymium glass and rhodium quartz filters respectively. Quartz 1 cm. cells were used for all compounds except the rubins; for these the 4 cm. cells were used.

McIlwain buffer solutions [4] of various pH values were prepared immediately before spectrophotometry from " AnalaR " chemicals in distilled carbon dioxide-free water which had passed through an Algastat Minor Type C 403 portable deioniser. They were stored in bottles coated internally with paraffin wax. Methanolic solutions of the compounds investigated were prepared in such concentrations that the addition of 0·5 ml. to 4 ml. of buffer solutions gave a solution with the optical density between 0·7 and 0·8 at the spectroscopic maxima. The same pipettes being used throughout, these volumes were transferred to 6" stoppered tubes, shaken, and immediately examined. After spectroscopy, the pH of each solution was determined on an E.I.L. 23A pH-meter, standardised as described in Part II of this series. Similar solutions prepared with 0·1N-hydrochloric acid, 0·1N-, 0·01N-, and 0·001N-sodium hydroxide were also examined, but the pH's of these were not confirmed potentiometrically. Solutions of urobilins prepared in this way were sufficiently stable to permit determination of complete spectral absorption curves over a wide range of pH (Fig. 2). With other pigments, particularly the verdins, solutions of pH 2—5 developed turbidity and then had lower optical density at the maxima. In such cases, complete spectral absorption curves were determined only for a few solutions, so as to establish the isosbestic points; at other pH values absorption at the maxima were rapidly determined, together with some at wavelengths close to and including the isosbestic point. Titration curves for the urobilins were also determined in this way, since prolonged contact with glass, and thus metal-complex formation at high pH, was avoided.

Veronal–acetate buffers of constant ionic strength (μ 0·1) were prepared from 0·18N-sodium chloride (" AnalaR ") and 0·12N-hydrochloric acid (" AnalaR ") and 0·06M-sodium acetate–sodium barbitone, the necessary volumes being calculated from the formulæ derived by Neuberger and Scott [5] and the Henderson–Hasselbach equation. Titration curves were determined with these buffers in the way described for the McIlwain buffers. These buffers were stored in Polythene bottles. With solutions so prepared, metal-complex formation by urobilins in alkaline solution did not occur.

Spectrophotometric titration curves were determined for different concentrations of stercobilin, d-urobilin, glaucobilin, biliverdin, the rubins, and the dipyrrylmethenes. No variation with concentration of pigment was observed.

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Department of Chemical Pathology, King's College Hospital Medical School, London, S.E.5. [*Received, October 20th*, 1960.]

[23] Kleinspehn, *J. Amer. Chem. Soc.*, 1955, **77**, 1547.
[24] Fischer and Morgenroth, *Annalen*, 1928, **466**, 165.
[25] Fischer and Hess, *Z. physiol. Chem.*, 1931, **194**, 209.

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443. *An Independent Confirmation of the Structure of Geijerene by Physical Methods.*

By A. J. Birch, J. Grimshaw, A. R. Penfold, N. Sheppard, and R. N. Speake.

The natural hydrocarbon geijerene, $C_{12}H_{18}$, is converted into isogeijerene by the action of potassamide in liquid ammonia. Examination of the ultraviolet, infrared, and nuclear magnetic resonance spectra of these compounds, and examination of the ions produced in the mass spectrometer from geijerene and hexahydrogeijerene permit assignment of the probable structure (VII) to geijerene. Some ancillary evidence provides further support for this structure, which has been independently proved by Sutherland.

The chemistry of geijerene, an optically inactive hydrocarbon, $C_{12}H_{18}$, from the essential oil of *Geijera parviflora* Lindley, was submitted to preliminary investigation by Penfold and Simonsen.[1] They showed it to be a monocyclic triene since it could be hydrogenated to hexahydrogeijerene, $C_{12}H_{24}$. Under milder conditions a tetrahydro-derivative was obtained containing $>C{=}CH_2$ since oxidation gave a ketone $C_{11}H_{20}O$. No aromatic compound could be detected after refluxing with selenium.

We began a further investigation in 1954 but, except for the reactions in liquid ammonia mentioned below, we had done little more than repeat the earlier experiments when we learned that Dr. M. D. Sutherland (Queensland) had made considerable progress with degradative work and this aspect was abandoned. We thought, however, that it would be of interest to see how far physical methods could be used to elucidate the structure of geijerene without recourse to chemical evidence relating it to known compounds.

At a stage of our work represented by formula (IV) and with several formulæ including (VII) and (VIII) under our consideration, Dr. Sutherland informed us that he had conclusively determined the structure (VII). We willingly concede priority to him in determination of the structure,[2] but most of the value of the present work is lost unless it is clear that we did in fact independently consider (VII), and we believe that work then in progress would in any case have led us to prefer this formula to the several other possibilities. Dr. Sutherland suggested simultaneous preliminary publication, but the present work could not be suitably condensed.

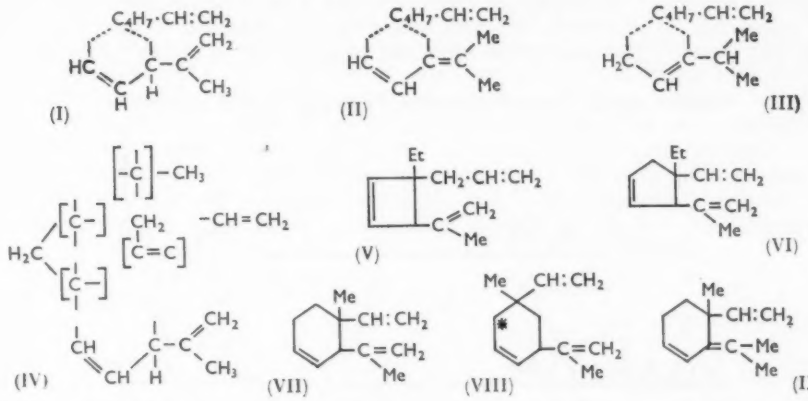
Ultraviolet Spectra.—Geijerene contains three double bonds which must be unconjugated since it has no selective ultraviolet absorption above 220 mμ. In view of its low molecular weight and cyclic nature we thought that there was a high probability of two double bonds being separated by only $>CH-$ or $-CH_2-$. If this were so, then they would become conjugated by the action of potassamide in liquid ammonia.[3] Conjugation in fact took place under these conditions, to give isogeijerene with $\lambda_{max.}$ 244 mμ (ε 8000) corresponding to a new *trans*-diene system. This isomer, or geijerene itself (presumably with preliminary conjugation), was reduced by potassium in liquid ammonia to a dihydroisogeijerene.

Infrared Spectra.—The spectrum of geijerene showed the presence of both $>C{=}CH_2$ ($\nu_{max.}$ 898 cm.$^{-1}$) and $-CH{=}CH_2$ ($\nu_{max.}$ 1005, 912 cm.$^{-1}$) groupings. Tetrahydrogeijerene retained the band due to $C{=}CH_2$ ($\nu_{max.}$ 895 cm.$^{-1}$), and the derived ketone, $C_{11}H_{20}O$, had the spectrum of a methyl ketone [3] ($\nu_{max.}$ 1712, 1365 cm.$^{-1}$). Geijerene, therefore, contained $-CH{=}CH_2$ and $-CMe{=}CH_2$ groups, and in accord with this assumption the spectrum of hexahydrogeijerene showed bands due to isopropyl ($\nu_{max.}$ 1392, 1375, 1173, 1155 cm.$^{-1}$) and methyl ($\nu_{max.}$ 1385 cm.$^{-1}$). The nature of the third double bond of geijerene remained uncertain for the moment, as there was no band of comparable strength which could be related to it.

[1] Penfold and Simonsen, *J. Proc. Roy. Soc. N.S.W.*, 1932, **66**, 332.
[2] Sutherland, *Chem. and Ind.*, 1959, 1220.
[3] Birch, *J.*, 1947, 1642.

Isogeijerene had lost the $>C=CH_2$ band but retained those due to $-CH=CH_2$ ($\nu_{max.}$ 1010, 903 cm.$^{-1}$) and showed a strong band probably due to a *cis*-CH=CH– group [4] ($\nu_{max.}$ 752 cm.$^{-1}$). From what is known of the type of reaction involved in the production of isogeijerene [3] it was unlikely that more than one double-bond movement occurred, so that the *cis*-CH=CH– was present in geijerene and therein related to the $-CMe=CH_2$ group as shown in (I). The spectrum of geijerene showed bands at $\nu_{max.}$ 700 and 785 cm.$^{-1}$ which can be ascribed [5] to this *cis*–CH=CH– group. Isogeijerene would then contain the structure (II), and this expectation was supported by the presence in dihydroisogeijerene of a trisubstituted double bond ($\nu_{max.}$ 815 cm.$^{-1}$) as well as the vinyl group ($\nu_{max.}$ 1008, 912 cm.$^{-1}$), indicating structure (III).

Since the early work of R. N. Jones and his colleagues [4,6] in the steroid field high-resolution infrared spectroscopy has been employed to a limited extent to distinguish



between methylene groups adjacent to, and removed from, unsaturated centres; presumably the two characteristic methyl-group frequencies suffer similar changes due to environment, but this does not appear to have been investigated in detail. Geijerene has five bands in the region 1400—1470 cm.$^{-1}$ ($\nu_{max.}$ 1413, 1436, 1446, 1452, 1460 cm.$^{-1}$) and two in the region 1360—1400 cm.$^{-1}$ ($\nu_{max.}$ 1370, 1375 cm.$^{-1}$) consistent with the presence of three types of methylene and two types of methyl group. This conclusion is to be classed as very highly probable rather than certain, since it is not impossible for a close pair such as the 1446—1452 cm.$^{-1}$ bands to be two components due to one group. In the subsequent discussion the frequency assignments made are based upon the literature previously cited and upon the review by Jones and Sandorfy.[7] An incorrect assignment would not affect the final conclusions which are based on the number of bands observed. One methyl group ($\nu_{max.}$ 1446, 1370 cm.$^{-1}$) is shown in formula (I), the other ($\nu_{max.}$ 1460, 1375 cm.$^{-1}$) is probably in a position not adjacent to a double bond. Formula (I) accommodates two $C=CH_2$ which contribute to one band ($\nu_{max.}$ 1413 cm.$^{-1}$) that probably overlaps the weak in-plane CH bending vibration of the *cis*-CH=CH– group. The remaining two bands probably correspond to $-CH_2-[C=C-]$ ($\nu_{max.}$ 1436 cm.$^{-1}$) and to $-CH_2-$ isolated from unsaturation (ν 1452 cm.$^{-1}$). If we allow the minimum number of groups in each class and take into account the previous deductions, we dispose of eleven carbon atoms and all of the hydrogen atoms in geijerene, and formula (I), can then be expanded to (IV).

[4] Jones, Cole, and Nolin, *J. Amer. Chem. Soc.*, 1952, **74**, 5662.
[5] Henbest, Meakins, and Wood, *J.*, 1954, 800; Allan, Meakins, and Whiting, *J.*, 1955, 1874.
[6] Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648; Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.
[7] Jones and Sandorfy, "Techniques of Organic Chemistry," Interscience Publ. Inc., New York, 1956, Vol. IX, p. 331.

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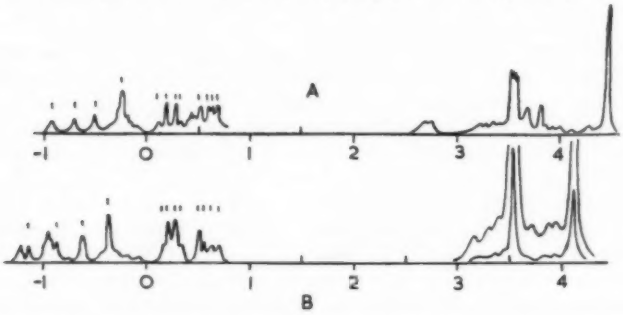
The remaining carbon atom must be quaternary if all our deductions are correct. The ring can also be four-, five-, or six-membered, so that formulæ of types (V), (VI), (VII), and (VIII) required consideration.

Nuclear Magnetic Resonance Spectra.—The chemical shift scale, σ, quoted below is based on an approximate water zero (see Experimental section). The main correlations between hydrocarbon structures and chemical shifts on this scale have been well summarised by Pople, Schneider, and Bernstein.[8]

The spectrum of geijerene itself (Fig. A) shows twelve lines (marked with vertical strokes) caused by the hydrogens of CH_2=CH- [C≡C_3] or CH_2=CH- , *i.e.*, of a vinyl group attached to a carbon atom carrying no other hydrogens. This whole pattern of lines is closely similar to, for example, that observed for the vinyl group of 3,3-dimethyl-1-butene by Alexander.[9] A conjugated diene structure is ruled out by the lack of ultraviolet absorption. These three hydrogen atoms have approximate σ values of −0·6, +0·25, and +0·63. The presence of additional olefinic =CH- is shown by bands at σ

Nuclear magnetic resonance spectrum of (A) *geijerene and* (B) *isogeijerene.*



−0·2, +0·15. The band at σ 2·73 corresponds to one or more hydrogens of the type [C=C]-CH- or [C=C]-CH-[C=C]. The strong band at σ 3·55 is probably due to CH_2 or Me of the type Me-[C=C]; the fine structure suggests interaction with 2H at the other end of the double bond, *i.e.*, that the grouping Me-C(H)=CH_2 is present. The strong band at σ 4·45 corresponds to Me-[C≡C_3]. We have already deduced that the vinyl group is attached to a quaternary carbon atom, and since the C_4H_7 residue of (I) can contain only one such carbon atom the molecule must contain Me-C[C_2]-CH=CH_2. The remaining complex band-structure in the region 3·2—4·0 corresponds to interacting CH or CH_2 groups in adjacent positions, some of these being adjacent to [C=C] (3·2—3·4).

In isogeijerene the 12-line vinyl pattern remains (Fig. B) although the quartet of the lone C≡CH is shifted to ~ −0·73. Olefinic CH additional to the vinyl group gives rise to doublet bands centred near −1·1 and a broad band near −0·3. The very strong and sharp band at 3·55 corresponds to Me-[C(C)=C] and because of its strength probably two such groups are present, as in Me_2C=C. The strong band at 4·15 indicates one Me of the type Me-[C≡C_3]. The same comments as for geijerene apply to the broad bands in the region 3·1—4·0.

There is nothing in the above deductions to contradict the conclusions drawn from the infrared spectra. In addition, they seem to rule out any formula containing an angular

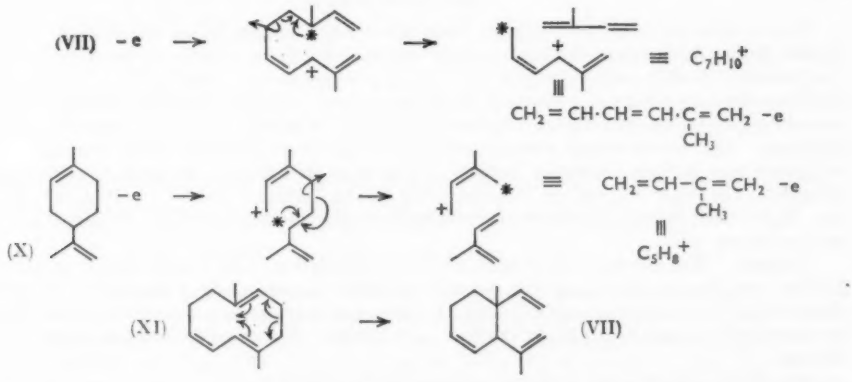
[8] Pople, Schneider, and Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959, Ch. 11.
[9] Alexander, *J. Chem. Phys.*, 1958, **28**, 358.

ethyl group; the remaining possibilities (VII) and (VIII) fit the data very well. The olefinic CH band in geijerene at −0·2 is probably due to $-CH=CH-$ and that in the region 0·5 to the $C=CH_2$ function of the $MeC(C)=CH_2$ group.

The structure (IX) also fits well the spectrum of isogeijerene; the group $Me_2C=C$ shows up particularly well. The fact that the $Me\cdot[C\equiv C_3]$ and $-CH=CH_2$ (vinyl) bands are both shifted considerably when compared with the spectrum of geijerene indicated that the ring substituents were probably adjacent, as in (VII), rather than separated, as in (VIII). The doublet of olefinic CH bands at −0·95 and −1·2 are probably caused by the $=CH-$ of the $-CH=CH-$ group which is adjacent to the conjugated double bond; the main separation is probably caused by strong spin–spin interaction with the other $-CH=$, and weak long-range coupling with the nearer of the two $-CH_2-$ groups could give rise to the unresolved triplet contours. Resonance of the other $-CH=$ of the $-CH=CH-$ would be expected to be more widely split, both by strong interaction with the immediately adjacent $-CH_2-$ group and by strong interaction with $=CH-$ at the other end of the double bond.

Evidence from the spectra of geijerene and isogeijerene was, therefore, strongly in favour of formula (VII) for the former. This was also supported by evidence of the hindered nature of the $-CMe=CH_2$ group in geijerene, as shown by its resistance to hydrogenation, and of the acetyl group in the ketone from tetrahydrogeijerene, as shown by its slow reaction with semicarbazide and failure [1] to lead to the bromoform reaction.

Mass Spectra.—Examination of the mass spectra (at 70 ev) of geijerene and hexahydrogeijerene confirmed the formulæ as $C_{12}H_{18}$ and $C_{12}H_{24}$, respectively, by peaks at the appropriate masses, small isotope peaks being obtained one unit higher. Structurally



the most significant peaks are those of large mass number, probably due to rupture of only one bond.[10] Saturated molecules are cleaved at the most highly substituted centres, an ethyl radical being lost in preference to a methyl; unsaturated molecules are cleaved at "allylic" bonds. Hexahydrogeijerene gave $C_{10}H_{19}^+$ as the most abundant heavy fragment. It must arise by loss of C_2H_5 from the quaternary carbon atom. At about one-third of this abundance was the ion $C_9H_{17}^+$, probably produced by loss of the isopropyl group. Ions of the groups C_7, C_8, and C_{11} were almost negligible in amount. The most abundant fragment was $C_6H_{11}^+$, and although explanations can be advanced to account for this no unequivocal structural conclusions could be drawn.

The most abundant fragment from geijerene larger than C_7 was $C_{11}H_{17}^+$ corresponding to loss of CH_3^-; only a trace of $C_{10}H_{15}^+$ was formed. This contrast with the hexahydrogeijerene results indicated the absence of an angular ethyl group in geijerene itself, but the presence of an allylic methyl group. The only major peaks (70 ev) corresponded to

[10] Field and Franklin, "Electron Impact Phenomena," Academic Press Inc., New York, 1957.

$C_6H_7^+$ and $C_7H_{10}^+$, and at 8 ev the former was greatly reduced and the latter greatly preponderant. The presence in the latter of an even number of hydrogen atoms indicated the loss of a molecule rather than a radical. Its formation was explicable on the basis of formula (VII) by the fissions shown above. Each arrow indicates the movement of one electron. Both fragments of the fission, the isoprene molecule and $C_7H_{10}^+$, should be stable, the latter representing the conjugated triene CH_2=CH–CH=CH–CMe=CH_2 minus one electron. An analogous observation was the production of $C_5H_8^+$ from limonene [11] (X).

The mass spectra indicated, therefore, the presence of allylic methyl, but not ethyl, in geijerene, and the presence of ethyl in hexahydrogeijerene, presumably generated by hydrogenation of –CH=CH_2. These observations and the production of $C_7H_{10}^+$ were explicable on the basis of either formula (VII) or (VIII) and were, therefore, in accord with our previous conclusions.

That a reasonably firm conclusion can be reached on the physical evidence cited was due partly to the relatively low molecular weight of geijerene and partly to the fact that no CH function is exactly duplicated anywhere in the molecule.

The optical inactivity of geijerene is unexpected in view of the presence of two asymmetric centres. By analogy with Ohaloff's results [12] on the conversion of a ten-membered ring compound, germacrone, into an elemane derivative merely by heat, it is possible that the precursor of geijerene is the analogous compound (XI). Geijerene could possibly be an artefact produced during prolonged rectification of the essential oil. Biogenetically geijerene is probably a sesquiterpene which has lost an isopropyl group.

Experimental

General Remarks.—Infrared spectra were taken on a Perkin-Elmer instrument model 21 (double-beam, double-pass sodium chloride prism) for CS_2 solutions, or on a model 112G (single-beam, double reflection grating) for CCl_4 solutions, as appropriate. Mass spectra were measured by means of a Metrovic Ms 2 instrument. Nuclear magnetic resonance spectra were measured by use of a Varian V-4300 spectrometer at 40 Mc. sec.$^{-1}$ for carbon tetrachloride solutions. The measurements were actually made against a benzene external standard. This resonance was in turn calibrated against cyclohexane as internal standard in carbon tetrachloride. The latter is given the value of +3·9 on the " water " scale: $\sigma = 10^6\Delta(H - H_r)/H_r$ ($r = H_2O$); for conversion to the tetramethylsilane internal standard scale (τ scale) [13] add 4·66 to all σ values.

Geijerene.—The essential oil obtained by steam-distillation of the foliage of *Geijera parviflora* Lindley was fractionated and the geijerene isolated as previously described.[14] It quickly deteriorated in air but was readily purified by percolation in pentane through alumina followed by distillation; it had b. p. 81—82°/14 mm., n_D^{23} 1·4910. It showed only end-absorption below 220 mμ.

Hexahydrogeijerene was prepared as previously described.[1]

Only one substance could be detected by vapour-phase chromatography of either geijerene or hexahydrogeijerene.

The mass spectrum of geijerene (70 ev) showed the following peaks >8% of largest peak (relative peak heights in parentheses): 27 (10·5); 39 (15·5); 41 (14·5); 77 (15·8); 79 (100); 91 (12·7); 93 (15); 94 (63); 147 (8·0); parent peak 162 (3·3).

The mass spectrum of hexahydrogeijerene (70 ev) showed the following peaks >10% of largest peak (relative peak heights in parentheses): 27 (17·7); 29 (20); 39 (14); 41 (52·5); 43 (30); 55 (69); 56 (19); 57 (40); 67 (11); 69 (81); 70 (42); 71 (17); 81 (11·5); 83 (100); 97 (18); 125 (14); 139 (38); parent peak 168 (4·35).

Isogeijerene.—Geijerene (1 g.) in ether (1·5 ml.) was added to potassamide (from potassium, 1 g.) in liquid ammonia (50 ml.), and the resulting crimson solution stirred for 15 min. Ethanol (3 ml.) was slowly added, followed by water, and the resulting *isogeijerene* separated and distilled

[11] Friedman and Wolf, *J. Amer. Chem. Soc.*, 1958, **80**, 2424.
[12] Ohaloff, *Angew. Chem.*, 1959, **71**, 162.
[13] Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.
[14] Penfold, *J. Proc. Roy. Soc. New South Wales*, 1930, **64**, 279.

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as a colourless oil, b. p. 87°/15 mm., n_D^{23} 1·52313, $\lambda_{max.}$ (in EtOH) 244 mμ (ε 8000) (Found: C, 88·6; H, 11·0. $C_{12}H_{18}$ requires C, 88·9; H, 11·1%).

Dihydroisogeijerene.—In separate experiments geijerene and isogeijerene (1 g.) in ether (5 ml.) were added to a solution of potassium (1 g.) in liquid ammonia (100 ml.). The solutions changed from red to blue and finally became colourless. *Dihydroisogeijerene*, isolated in the usual way, was a colourless oil, b. p. 80°/13 mm., showing only end-absorption in the ultraviolet spectrum (Found: C, 87·4; H, 12·1. $C_{15}H_{20}$ requires C, 87·8; H, 12·2%).

Apotetrahydrogeijerene.—Hydrogenation of geijerene over 2% palladium–strontium carbonate ceased after uptake of 2 mols.[1] Ozonolysis of the tetrahydrogeijerene was carried out as previously described.[1] The semicarbazone of the product was formed slowly, unchanged ketone being detectable even after 1 hour's heating on the steam-bath with an excess of semicarbazide acetate in aqueous methanol. The semicarbazone formed colourless plates, m. p. 167—168° (lit.,[1] 163—164°) (Found: C, 64·3; H, 9·7. Calc. for $C_{12}H_{23}N_3O$: C, 64·0; H, 10·3%). The ketone was regenerated from this derivative by steam-distillation from N-sulphuric acid for spectral examination.

This work was carried out during the tenure of an I.C.I. Fellowship (J. G.) and a D.S.I.R. Research Scholarship (R. N. S.). We are greatly indebted to Dr. J. G. Watkinson and Dr. G. D. Meakins for measurements of infrared spectra and for discussions on their interpretation, and to Dr. J. H. Baxendale and Dr. R. I. Reed for measurements and discussion of mass spectra. The nuclear magnetic resonance spectrometer was presented to the University Chemical Laboratory, Cambridge, by the Wellcome Foundation.

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444. *Acetylenic Compounds Related to Stilbœstrol. Part IV.*[1] *The Preparation of α-Alkyl-β-ethynyl-4,4′-dihydroxystilbenes.*

By C. W. Shoppee, J. Cymerman Craig, and Ruth E. Lack.

Although attempted demethylation of 1,2-di-(*p*-methoxyphenyl)but-1-en-3-yne (IIa) led to decomposition, use of the 1,2-di-(*p*-tetrahydropyranyloxyphenyl)-derivative, obtained from 4,4′-bis(tetrahydropyranyloxy)deoxybenzoin and ethynylmagnesium bromide, gave 1,2-di-(*p*-hydroxyphenyl)-but-1-en-3-yne.

Conversion of 4,4′-dibenzoyloxy-α-ethyldeoxybenzoin into the acetylenic alcohol (Ia) was accomplished with preservation of the benzoate groups. Attempted dehydration of the alcohol (Ia) with phosphorus trichloride in pyridine or triethylamine gave only insoluble phosphate esters, but use of thionyl chloride in triethylamine afforded the chloroallene (Va), the chloroacetylene (IX), and the *trans*-isomer of 1,2-di-(*p*-benzoyloxyphenyl)hex-1-en-3-yne (IIc), whose structure was proved by hydrogenation to stilbœstrol dibenzoate.

Preceding papers of this series[1] have described methods for obtaining 1-alkyl-1,2-di-(*p*-methoxyphenyl)but-3-yn-2-ols (as Ib) and 1-alkyl-1,2-di-(*p*-methoxyphenyl)but-1-en-3-ynes (as IId). The preparation of the corresponding phenolic compounds has now been investigated.

Preliminary experiments showed that demethylation of compounds of type (Ib) and

[1] Shoppee, Craig, and Lack, Part III, *J.*, 1961, 1311.

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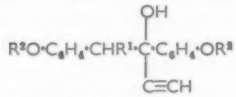
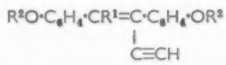
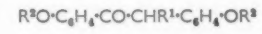
(IId) with alcoholic alkali [2] or with hydriodic acid [3,4] at high temperatures caused extensive decomposition of the acetylenic compounds; whilst the use of aluminium bromide in benzene [5] or in collidine [6] (172°) also failed.



(I) a: R^1 = Et, R^2 = Bz
b: R^1 = Et, R^2 = Me



(II) a: R^1 = H, R^2 = Me
b: R^1 = H, R^2 = Ac
c: R^1 = Et, R^2 = Bz
d: R^1 = Et, R^2 = Me



(III) a: R^1 = R^2 = H
b: R^1 = H, R^2 = tetrahydropyran-2-yl
c: R^1 = Et, R^2 = Bz
d: R^1 = Et, R^2 = Me
e: R^1 = H, R^2 = Bz
f: R^1 = Et, R^2 = H

Attempted demethylation of 1,2-di-(*p*-methoxyphenyl)but-1-en-3-yne (IIa) by aluminium bromide in xylene (140°) gave no phenolic material after 2 hr., but extensive polymerisation of the starting material occurred to give the known dimeric product.[1] The instability of acetylenic stilbenes of type (II) to both acidic reagents and temperatures above 140° thus required use of protecting groups, other than methoxyl, removable under milder conditions; tetrahydropyranyl ethers proved satisfactory.

The preparation of 4,4′-dihydroxydeoxydenzoin has been described,[7] by the action of boiling water on the diazonium salt from 4,4′-diaminotolan or 4,4′-diaminodeoxybenzoin. Treatment of the readily accessible deoxyanisoin [8] with hydriodic acid in the presence of either phenol or acetic acid gave excellent yields of 4,4′-dihydroxydeoxybenzoin (IIIa). Anisoin with hydriodic acid in phenol gave also 4,4′-dihydroxydeoxybenzoin.

4,4′-Dihydroxydeoxybenzoin was converted into its bistetrahydropyranyl ether (IIIb) in 93% yield by a modification of Parham's method [9] in the absence of solvents. Addition of sodium hydroxide at the end of the reaction was essential to prevent hydrolysis to the starting phenol, whilst the use of dioxan resulted in considerably reduced yields (cf. ref. 10) and isolation of appreciable quantities of the hydrolysis product δ-hydroxyvaleraldehyde. Treatment of the bistetrahydropyranyl ether (IIIb) with ethynylmagnesium bromide [11] gave solely phenolic material, consisting of a mixture of ketone and alcohol which decomposed on chromatography. Alternatively, the product was converted, after removal of unchanged ketonic material by Girard's reagent D,[12] directly into the stilbene diacetate (IIb). Its ultraviolet spectrum showed absorption characteristic of the *trans*-stilbene chromophore and was transformed, on irradiation of the compound, into that of the *cis*-isomer with the previously observed [1] changes in intensities (cf. Table).

Demethylation of α-ethyldeoxyanisoin [1] by hydriodic and acetic acids, as described by Dodds *et al.*,[4] gave a product consisting mainly of 1-*p*-hydroxyphenyl-2-*p*-methoxyphenylbutan-1-one which on further treatment with the same reagent afforded the known amorphous 4,4′-dihydroxy-α-ethyldeoxybenzoin.[4]

Reaction of the dibenzoate (IIIc) with a large excess of ethynylmagnesium bromide in

[2] Salzer, *Z. physiol. Chem.*, 1942, **5**, 39; Biggerstaff and Wilds, *J. Amer. Chem. Soc.*, 1949, **71**, 2132; Spath, *Monatsh.*, 1914, **35**, 319.
[3] Dodds, Golberg, Lawson, and Robinson, *Nature*, 1938, **142**, 1121; La Forge, *J. Amer. Chem. Soc.*, 1933, **55**, 3040.
[4] Dodds, Golberg, Lawson, and Robinson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 140.
[5] Burckhalter and Sam, *J. Amer. Chem. Soc.*, 1952, **74**, 187.
[6] Marshall and Whiting, *J.*, 1957, 537.
[7] Zincke and Fries, *Annalen*, 1902, **325**, 75.
[8] Carter, Craig, Lack, and Moyle, *J.*, 1959, 476.
[9] Parham and Anderson, *J. Amer. Chem. Soc.*, 1948, **70**, 4187; Parham and De Laitsch, *ibid.*, 1954, **76**, 4962.
[10] Gaspert, Halsall, and Willis, *J.*, 1958, 624; Cocker and Halsall, *J.*, 1957, 3441.
[11] Jones, Skattebol, and Whiting, *J.*, 1956, 4765.
[12] Viscontini and Meier, *Helv. Chim. Acta*, 1950, **33**, 1773.

Ultraviolet absorption spectra.

Compound	$\lambda_{max.}$ (mμ)	ε	Compound	$\lambda_{max.}$ (mμ)	ε
(IIb): *trans*	230, 315	15,550, 28,000	(IId): *trans* ...	223, 284	14,600,12,200
(IIb): *cis*	234, 302	17,900, 17,800	Stilbœstrol di-		
(IIc): *trans*	232, 272	50,800, 25,350	benzoate	232, 270 infl.	34,600, 12,000
(IIc): *cis*	232, 270 infl.	58,000, 24,800	(Va)	233, 260	47,600, 29,000
			(Vb)	224, 278	18,100, 14,900

tetrahydrofuran under reflux (66°) gave a phenolic product which on re-benzoylation yielded the acetylenic alcohol (Ia): there was extensive decomposition and the neutral fraction contained only polymeric material. At 0° the Grignard reaction gave no phenolic product, and the neutral portion consisted of a mixture of the acetylenic alcohol (Ia) with unchanged starting material. When the reaction period (2 hr. at 0°) was extended (72 hr. at 20°) considerable decomposition ensued, but an excellent yield of the alcohol (Ia), free from starting ketone and decomposition products, was obtained by interaction for 2 hr. at 0° with a further 2 hr. at 20° only.

It is noteworthy that the 4,4′-dibenzoyloxy-grouping is retained even in the presence of a large excess of the Grignard reagent at 0° and 20°, while refluxing resulted in the removal of the ester groups. The same dibenzoate was found [4] to be converted entirely into the phenolic tertiary alcohol by refluxing with ethereal ethylmagnesium bromide. While the related α-ethyldeoxyanisoin (IIId) required 18 hours' refluxing (66°) to react with ethynylmagnesium bromide,[1] the 4,4′-dibenzoyloxy-compound (IIIc) was completely converted into the tertiary alcohol (Ia) under the mild conditions (0° to 20°) described above. This difference in the reactivity of the carbonyl function in these two ketones is due to the greater electron-withdrawing effect of the *p*-benzoyloxy- than of the *p*-methoxy-group. Contributions from resonance structures such as (IVa), which will reduce the reactivity of the carbonyl carbon atom in (III), will be large in the case of the *p*-methoxy- but small in that of the *p*-benzoyloxy-ketone, because of the alternative resonance possibilities in the benzoyloxy-system (IVb).

Attempted dehydration of the acetylenic alcohol (Ia) by means of phosphorus trichloride in pyridine [1] at −20°, which gave the chloroallene (Vb) from the corresponding di-(*p*-methoxyphenyl) compound, gave only a low yield of an ether-soluble product, shown to contain the chloro-allene (Va), $\nu_{max.}$ 1930 cm.$^{-1}$, and the αβ-unsaturated ketone (VI), $\nu_{max.}$ 1670 cm.$^{-1}$. The major portion of the product was ether-insoluble and appeared to consist of phosphate esters. Use of phosphorus trichloride in triethylamine at −40° again gave a phosphate ester which resisted alkaline or acid hydrolysis and was not further investigated.

The different behaviour of the *p*-benzoyloxyphenyl compound (Ia) and its *p*-methoxyphenyl analogue may again be due to the electron-withdrawal inequality *p*-BzO > *p*-MeO, leaving an electron-deficiency on the α-carbon atom in the former case and thus preventing the fission of the C–O bond shown [1] to occur in the latter case.

The acetylenic alcohol (Ia), when treated with thionyl chloride in triethylamine at −40° for 0·5 hr., afforded the chloro-allene (Va), $\nu_{max.}$ 1925 and 1890 cm.$^{-1}$ (conjugated C=C=C) and 753 and 740 cm.$^{-1}$ (C–Cl), the desired *trans*-3,4-di-(*p*-benzoyloxyphenyl)hex-3-en-1-yne (IIc) (changed by irradiation to the *cis*-isomer; see Table), and the αβ-unsaturated ketone (VI), m. p. 156°, formed by the Meyer–Schuster rearrangement previously discussed.[1] When an improved chromatographic technique was employed in a similar experiment, in which treatment with thionyl chloride was for only 5 min. at

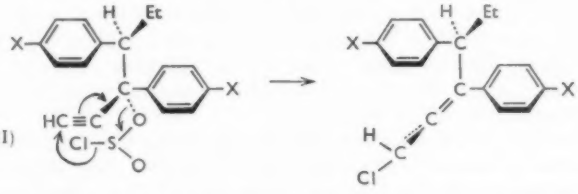
—40°, the products were the chloro-allene (Va), the chloro-acetylene (IX), and the

(V) a: R = Bz RO·C_6H_4·CHEt·C(=C=CHCl)·C_6H_4·OR BzO·C_6H_4·CEt=C(COMe)·C_6H_4·OBz (VI)
b: R = Me

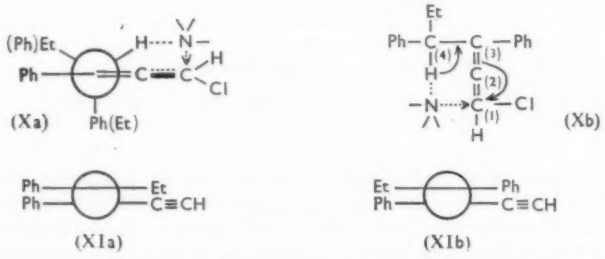
(VII) BzO·C_6H_4·CHEt·C(=CH·CHO)·C_6H_4·OBz BzO·C_6H_4·CHEt·CCl(C≡CH)·C_6H_4·OBz (IX)

trans-stilbene (IIc): absence of the ketone (VI) may be ascribed to the fact that alkaline conditions were preserved during the working-up. The reaction with thionyl chloride presumably proceeds through the chlorosulphite (VIII).[13] It is known that the halogen atom in ester halides formed from phosphorus or thionyl halides is easily ionised and can,

(VIII)



by a unimolecular or bimolecular process, give the chloro-compound (IX) by attack on the oxygen-bearing carbon atom.[13] In the chlorosulphite ester (VIII), however, this carbon atom is in a highly hindered environment of a t-butyl nature. Molecular models show that the halogen atom is close to the terminal carbon atom of the ethynyl group, and attack of the halogen on this carbon atom also occurs, with the concerted electron-shifts shown in (VIII), resulting in the simultaneous formation of the chloro-allene (Va) and elimination of sulphur dioxide. That only a trace of the chloroallene was obtained when phosphorus trichloride was employed as the reagent agrees with the known lower tendency of chlorophosphates than of chlorosulphites to rearrange.[13]



The process, whereby dehydrohalogenation of the chloro-allene (Vb) gave both the *cis*- and the *trans*-form of the ethynyl-stilbene (IId) may be envisaged as the concerted elimination (Xb), in which attack by the tertiary nitrogen atom, from the direction indicated, on the terminal carbon atom of the chloroallene group results in ionisation of the chlorine atom and loss of a proton from $C_{(4)}$ to give either of the two possible stilbenes (XIa) and (XIb). The same products would result if the intermediate chloroallene existed in the diastereoisomeric form shown in parentheses in (Xa). Only the *trans*-form of the stilbene (IIc) could be isolated, however, on treatment of the alcohol (Ia) with thionyl chloride in triethylamine.

Treatment of the chloroallene (Va) with sodamide in liquid ammonia gave a completely phenolic product, which after rebenzoylation was shown to contain a small proportion of an acetylenic substance but was mainly an αβ-unsaturated carbonyl compound, m. p. 193°, isomeric with the ketone (VI) of m. p. 156° previously obtained, and believed to be the aldehyde (VII), formed by the Rupe rearrangement.[1]

[13] Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252.

The considerable steric hindrance at the central double bond of αβ-disubstituted stilbenes is shown by their ultraviolet absorption spectra, in which interference between both pairs of alkyl and aryl groups has largely destroyed the coplanarity of the chromophoric system,[14] resulting in a lower intensity, and a shift to shorter wavelengths, of the absorption maximum in the 230—240 mμ region with increasing size of the αβ-substituents.[15] The dibenzoyloxy-compound (IIc) showed a main absorption band at 232 mμ, much more intense than that of the dimethoxy-compound (IId) and the second (weaker) band was shifted from 284 to 272 mμ.[1] The same shifts are shown by the chloroallenes (V), where the 4,4′-dibenzoyloxy-compound had high-intensity absorption at 233 and 260, and the 4,4′-dimethoxy-analogue [1] at 224 and 278 mμ.

It is known that the hindered olefinic linkage in stilbœstrol required greatly prolonged reaction periods [4] for catalytic hydrogenation, and we found that stilbœstrol dibenzoate was recovered unchanged after attempted hydrogenation with platinum oxide in ethyl acetate. Under the same conditions, the 4,4′-dibenzoyloxystilbene (IIc) was reduced smoothly to stilbœstrol dibenzoate, the central double bond proving resistant to further hydrogenation; the structure of the acetylenic stilbene (IIc) is thus confirmed.

Experimental

M. p.s were determined on a Kofler block (error ±2°). Ultraviolet absorption spectra were determined for 95% EtOH solutions on a Hilger " Uvispek " instrument, and infrared spectra on a Perkin–Elmer " Infracord " spectrophotometer. Aluminium oxide used was Woelm (neutral) or Spence type H, activity II (alkaline).

Attempted Demethylation of 1,2-*Di*-(p-*methoxyphenyl*)*but*-1-*en*-3-*yne* (IIa).—1,2-Di-(*p*-methoxyphenyl)but-1-en-3-yne (100 mg.) was treated with aluminium bromide (500 mg.) in xylene (10 ml.) at 140° for 2 hr. or in benzene (10 ml.) at 80° for 5 hr. Extraction with sodium hydroxide solution gave no phenolic material whilst evaporation of the washed and dried solvent layer at 80° under reduced pressure gave dark polymers, m. p. 140—150°.

4,4′-*Dihydroxydeoxybenzoin* (IIIa).—(*a*) Deoxyanisoin (60 g.) was treated with 50% aqueous hydrogen iodide (200 ml.) and phenol (40 g.) for 0·5 hr. at the b. p. (cf. La Forge [3]). After removal of phenol in steam the product was extracted into ether, washed with sodium hydrogen sulphite and sodium hydrogen carbonate solution, dried, and evaporated. The pink solid recrystallised from aqueous ethanol, to give 4,4′-dihydroxydeoxybenzoin as colourless prisms (49·6 g., 93·5%), m. p. 217°, $\lambda_{max.}$ 222, 280 mμ (ε 24,130 and 24,130), $\nu_{max.}$ 3490, 3390 (OH), 1670 (C=O) cm.$^{-1}$ [Found (after drying at 20°/1 mm. for 16 hr.): C, 73·4; H, 5·4; O, 21·0. Calc. for $C_{14}H_{12}O_3$: C, 73·65; H, 5·3; O, 21·0%]. Zincke and Fries [7] give m. p. 214°.

(*b*) Treating deoxyanisoin (20 g.) with 50% hydrogen iodide (65 ml.) and phenol (27 g.) gave 4-*hydroxy*-4′-*methoxydeoxybenzoin* (12·5 g.), m. p. 157°, $\lambda_{max.}$ 222, 279 mμ (ε 21,200 and 18,800), $\nu_{max.}$ 3440 (OH), 1668 (C=O) cm.$^{-1}$ [Found (after drying at 50°/1 mm. for 6 hr.): C, 74·2; H, 5·8; OMe, 12·6. $C_{15}H_{14}O_3$ requires C, 74·35; H, 5·85; OMe, 12·8%].

(*c*) Hydriodic acid (50 ml.; *d* 1·7) and deoxyanisoin (10 g.) in acetic acid (10 ml.) were heated at 135—140° for 10 min. The cooled solution was poured into water and clarified with sodium hydrogen sulphite, and the precipitate was filtered off, to give 4,4′-dihydroxydeoxybenzoin (9·0 g.), m. p. 217°.

(*d*) Anisoin (5 g.) was treated with hydriodic acid (*d* 1·7, 25 ml.) and phenol (3·5 g.) for 0·5 hr. under reflux. After removal of phenol by steam distillation, the product was ether extracted to give 4,4′-dihydroxydeoxybenzoin, m. p. and mixed m. p. 217°.

(*e*) 4,4′-Dihydroxydeoxybenzoin (IIIa) (500 mg.) in 5% aqueous sodium hydroxide (5 c.c.) was treated with benzoyl chloride (500 mg.) at 0°. Recrystallisation of the white solid from ethyl acetate gave 4,4′-*di*-(p-*benzoyloxy*)*deoxybenzoin* (IIIe), m. p. 183°, $\lambda_{max.}$ 238 mμ (ε 27,000), $\nu_{max.}$ 1740 (benzoate), 1690 (C=O) cm.$^{-1}$ [Found (after drying at 40°/1 mm. for 6 hr.): C, 76·8; H, 4·7. $C_{28}H_{20}O_5$ requires C, 77·05; H, 4·6%].

Treatment of 4,4′-*Dihydroxydeoxybenzoin with Dihydropyran.*—(*a*) 4,4′-Dihydroxydeoxybenzoin (10 g.), dried at 100° for 24 hr., in redistilled dihydropyran (20 c.c.) was heated with

[14] Braude, *J.*, 1949, 1902.
[15] Suzuki, *Bull. Chem. Soc. Japan*, 1952, **25**, 145; Oki, *ibid.*, 1953, **26**, 37, 161, 331.

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16N-hydrochloric acid (3 drops) at 50° until a clear solution resulted; N-sodium hydroxide (10 ml.) was added to the mixture, which solidified after 1 hr. at 20°. Filtration gave 4,4′-*bistetrahydropyran*-2-*yloxydeoxybenzoin* (IIIb) (16·2 g.) (93%), m. p. 125°, $\lambda_{max.}$ 222, 273 mμ (ε 17,000 and 17,000), $\nu_{max.}$ 1685 (C=O) cm.$^{-1}$ [Found (after drying at 20°/1 mm. for 4 hr.): C, 72·55; H, 7·0. $C_{34}H_{36}O_5$ requires C, 72·7; H, 7·1%].

(*b*) 4,4′-Dihydroxydeoxybenzoin (2·5 g.) in dry dioxan (20 ml.) was treated with 16N-hydrogen chloride (3 drops). Dihydropyran (1·85 g.) was added and the mixture left at 25° for 18 hr. Ether was added and the phenolic material extracted with sodium hydroxide. Evaporation of the ether layer left an oil, b. p. 55—57°/5 × 10^{-3} mm., which by treatment with 2,4-dinitrophenylhydrazine gave δ-*hydroxyvaleraldehyde* 2,4-*dinitrophenylhydrazone*, m. p. 115°, identical with a sample prepared from dihydropyran [Found (after drying at 20°/1 mm. for 4 hr.): C, 47·1; H, 5·3. $C_{11}H_{14}O_5N_4$ requires C, 46·8; H, 5·0%]. The residue crystallised from ethanol to give 4,4′-bistetrahydropyran-2-yloxydeoxybenzoin (IIIb) (500 mg.), m. p. and mixed m. p. 125°. Acidification of the alkaline layer followed by ether extraction gave unchanged 4,4′-dihydroxydeoxybenzoin (1·7 g.), m. p. 215°.

Treatment of 4,4′-*Bistetrahydropyran*-2-*yloxydeoxybenzoin with Ethynylmagnesium Bromide.*—The bistetrahydropyranyl ether (IIIb) (4 g.) was treated with an excess of ethynylmagnesium bromide [1] at 0°, and the mixture refluxed for 3 hr. and kept at 20° for 1·5 hr. After the usual isolation the brown oil (3·5 g.) was treated with Girard reagent D (2 g.) in ethanol (20 ml.) and acetic acid (2·0 g.) at 100° for 0·5 hr. The solution was poured into ice-water (200 ml.) containing enough potassium carbonate (2·07 g.) to neutralize 90% of the acid present. Benzene extracted an oil that was immediately treated with acetic anhydride (5 ml.) at 100° for 10 min. The dark brown mixture was extracted with ether, and the extract washed with sodium hydrogen carbonate solution, and evaporated to give a brown oil (3 g.), which was adsorbed on a column of aluminium oxide (90 g.) in hexane. Elution with hexane (3 × 20 ml.) and benzene–hexane (5 : 1; 7 × 20 ml.) gave 1,2-*di*-(p-*acetoxyphenyl*)*but*-1-*en*-3-*yne* (IIb) (1·3 g.), m. p. 142°, $\nu_{max.}$ 3220 (C≡CH), 2150 (C≡C), 1740 cm.$^{-1}$ (C=O in Ac), $\lambda_{max.}$ 230, 315 mμ (ε 15,550 and 28,000) [Found (after drying at 20°/1 mm. for 3 hr.): C, 74·8; H, 5·15; O, 20·6; active H, 0·3. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·0; O, 20·0; active H, 0·3%]. After being kept in sunlight for 12 hr., it had $\lambda_{max.}$ 234, 302 mμ (ε 17,900 and 17,800). The ketone layer from the Girard separation was acidified with hydrochloric acid to give 4,4′-dihydroxydeoxybenzoin (IIIa), m. p. and mixed m. p. 216°.

α-*Ethyl*-4,4′-*dihydroxydeoxybenzoin* (IIIf).—Hydriodic acid (300 ml.; *d* 1·7) and α-ethyldeoxyanisoin (60 g.) in acetic acid (60 ml.) were gradually heated to 135—140° and kept at this temperature for 15 min., then poured into water and extracted with ether. The ether layer was decolorised with sodium hydrogen sulphite solution, extracted with N-sodium hydroxide, and evaporated, giving unchanged α-ethyldeoxyanisoin (7·5 g.). Acidification of the alkaline layer followed by ether-extraction gave mainly 1-p-*hydroxyphenyl*-2-p-*methoxyphenylbutan*-1-*one* (50 g.), m. p. 105—109° [Found (after drying at 20°/1 mm. for 3 hr.): C, 74·9; H, 6·8; OMe, 10·4. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7; OMe, 11·7%].

This product (50 g.) was treated with hydriodic acid (200 ml.; *d* 1·7) in acetic acid (60 ml.) at 140° for 10 min. Isolation in the usual way gave amorphous α-ethyl 4,4′-dihydroxydeoxybenzoin (42 g.) [dibenzoate,[4] m. p. 137—138°, $\lambda_{max.}$ 236 mμ (ε 23,500)].

3,4-*Di*-(p-*benzoyloxyphenyl*)*hex*-1-*yn*-3-*ol* (Ia).—(*a*) Ethylmagnesium bromide (from ethyl bromide, 22 ml., 0·3 mol., and magnesium, 6 g., 0·25 mol.) in tetrahydrofuran (100 ml.) was slowly added to a large excess of acetylene in tetrahydrofuran (100 ml.) at 0°. 1,2-Di-(*p*-benzoyloxyphenyl)butan-1-one (IIIe) (23·2 g., 0·05 mol.) was added at 0° and the mixture refluxed for 2 hr. The dark brown solid product obtained by decomposition with ammonium chloride and acidification with 2N-sulphuric acid, was extracted with ether. The extract was washed with sodium hydrogen carbonate, and the phenolic product was removed in 2N-sodium hydroxide, and recovered by acidification and ether-extraction. It formed a dark brown oil (15 g.), which, after treatment with benzoyl chloride (15 g.) in 2N-sodium hydroxide, was adsorbed on aluminium oxide (500 g.) in hexane. Elution with benzene gave dark amorphous material (4·63 g.); elution with ether–benzene (1 : 1; 3 × 100 ml.) and ether (6 × 100 ml.) afforded 3,4-*di*-(p-*benzoyloxyphenyl*)*hex*-1-*yn*-3-*ol* (Ia) (9·4 g.), m. p. 170—171°, $\lambda_{max.}$ 230 mμ (ε 43,000), inflexion 270 mμ (ε 8000), $\nu_{max.}$ 3480 (OH), 3300 (C≡CH), 1750, 1270, and 1160 cm.$^{-1}$ (benzoate) [Found (after drying at 20°/1 mm. for 2 hr.): C, 78·2; H, 5·55. $C_{32}H_{26}O_5$ requires C, 78·35; H, 5·55%].

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(*b*) 1,2-Di-(*p*-benzoyloxyphenyl)butan-1-one (IIIc) (4·64 g.) was treated with ethynylmagnesium bromide (from ethyl bromide, 4·5 ml., and magnesium, 1·2 g.) in tetrahydrofuran (75 ml.) at 0° for 1·5 hr. The usual working-up gave a pale yellow oil (5·2 g.) from which unchanged ketone (2·5 g.), m. p. 136°, separated on the addition of ethanol; removal of the solvent gave a yellow oil which was chromatographed on aluminium oxide (60 g.) in hexane. Elution with benzene (5 × 50 ml.) gave 3,4-di-(*p*-benzoyloxyphenyl)hex-1-yn-3-ol (2·15 g.), m. p. and mixed m. p. 171°.

(*c*) When the ketone (IIIc) was treated with ethynylmagnesium bromide at 0° for 2 hr. and 20° for 72 hr., it gave a dark phenolic product from which no pure compound was isolated.

(*d*) Di-(*p*-benzoyloxyphenyl)butan-1-one (IIIc) (23·2 g.) was treated with ethynylmagnesium bromide (from ethyl bromide, 22 ml., and magnesium, 6 g.) in tetrahydrofuran (150 ml.) at 0°, and the mixture was stirred for 2 hr. at 0° and for 2 hr. at 20°. Decomposition of the complex followed by ether-extraction gave 3,4-di-(*p*-benzoyloxyphenyl)hex-1-yn-3-ol (Ia) (19·8 g.), m. p. and mixed m. p. 170—171°.

Dehydration of 3,4-*Di*-(p-*benzoyloxyphenyl*)*hex*-1-*yn*-3-*ol* (Ia).—(*a*) The alcohol (Ia) (2 g.) in pyridine (20 ml.) was treated with phosphorus trichloride (2 ml.) at −20° for 5 hr. The mixture was poured into ice-water and extracted with ether. The extract was filtered from phosphorus esters and evaporated, yielding a yellow oil (200 mg.), $\nu_{max.}$ 1930 (C=C=C), 1740 (OBz) and 1670 (C=C–C=O) cm.$^{-1}$.

(*b*) The alcohol (Ia) (1 g.) in triethylamine (5 ml.) and tetrahydrofuran (5 ml.) was treated with phosphorus trichloride (2 ml.) at −40° for 5 min. The mixture was poured on ice and extracted with methylene dichloride. The extract was washed with ice-cold N-sodium hydroxide, N-sulphuric acid, and then immediately with sodium hydrogen carbonate solution. Evaporation of the solvent gave a product which did not crystallise, but reprecipitation from benzene with pentane gave a pale yellow amorphous solid, m. p. 140—142°, containing phosphorus (ammonium molybdate test) [Found (after drying at 50°/1 mm. for 6 hr.): C, 60·6; H, 5·4; O, 16; residue, *ca.* 16%]. This material is considered to be a stable phosphorus ester and was not further investigated.

(*c*) The alcohol (Ia) (2 g.) in tetrahydrofuran (20 ml.) and triethylamine (30 ml.) was treated with thionyl chloride (2 ml.) at −40°. After 0·5 hr. at 0° the product was poured on ice and extracted with ether, and the extracts were washed as in (*b*). Evaporation gave a product, m. p. 95—110°, which was adsorbed from hexane–benzene on aluminium oxide (40 g.) prepared in hexane. Elution with benzene–hexane (1 : 20; 3 × 50 ml.) gave 1-*chloro*-3,4-*di*-(p-*benzoyloxyphenyl*)*hexa*-1,2-*diene* (Va) (450 mg.), m. p. 96—97°, $\lambda_{max.}$ 233, 260 mμ (ε 47,600 and 29,000), $\nu_{max.}$ (in CS_2) 1925, 1890 (C=C=C), 1740 (OBz), 740, 753 (CCl) cm.$^{-1}$ [Found (after drying at 20°/1 mm. for 4 hr.): C, 75·5; H, 4·95. $C_{32}H_{25}O_4Cl$ requires C, 75·5; H, 4·95%]. Further elution with benzene–hexane gave crystals shown by infrared analysis to be a mixture of allenic and acetylenic material. Elution with benzene gave trans-3,4-*di*-(p-*benzoyloxyphenyl*)-*hex*-3-*en*-1-*yne* (IIc) (102 mg.), m. p. 185—187°, $\lambda_{max.}$ 232, 272 mμ (ε 50,800, 25,350) changing in 24 hr. in sunlight to 232 mμ (ε 58,600), inflexion *ca.* 270 mμ (ε 24,800), $\nu_{max.}$ (in CS_2) 3300 (C≡CH) and 1740 cm.$^{-1}$ (OBz) [Found (after drying at 20°/1 mm. for 48 hr.): C, 79·8; H, 5·35; O, 14·5. $C_{32}H_{24}O_4,\frac{1}{2}H_2O$ requires C, 79·8; H, 5·25; O, 14·95%]. Elution with ether–benzene (1 : 10; 2 × 50 ml.) and ether (5 × 50 ml.) gave 3,4-*di*-(p-*benzoyloxyphenyl*)*hex*-3-*en*-2-*one* (VI) (460 mg.), colourless needles (from ethanol), m. p. 156° (positive iodoform reaction), $\lambda_{max.}$ 232 mμ (ε 58,000), inflexion *ca.* 270 mμ (ε 23,000), $\nu_{max.}$ 1740 (OBz), 1650 (C=C–C=O) cm.$^{-1}$ [Found (after drying at 20°/1 mm. for 4 hr.): C, 78·6; H, 5·9. $C_{32}H_{26}O_5$ requires C, 78·35; H, 5·35%].

(*d*) The alcohol (Ia) (2 g.) was treated with thionyl chloride as in (*c*) but for only 5 min. at −40°; the mixture was poured into ice-cold N-sodium hydroxide, and the product isolated in the usual manner to give an oil. This was adsorbed on aluminium oxide (60 g.) prepared in hexane. Elution with benzene–hexane (1 : 20; 3 × 50 ml.) gave the chloroallene (Va) (620 mg.), m. p. and mixed m. p. 95—97°; further elution with benzene–hexane (1 : 5; 5 × 50 ml.) gave 3-*chloro*-3,4-*di*-(p-*benzoyloxyphenyl*)*hex*-1-*yne* (IX) (150 mg.), m. p. 130°, $\lambda_{max.}$ 232 mμ (ε 58,500), $\nu_{max.}$ (in CS_2) 3300 (C≡CH) and 1740 cm.$^{-1}$ (OBz) [Found (after drying at 20°/1 mm. for 8 hr.): C, 75·65; H, 4·9; active H, 0·17. $C_{32}H_{25}ClO_4$ requires C, 75·5; H, 4·95; active H, 0·19%]. Further elution with benzene gave *trans*-3,4-di-(*p*-benzoyloxyphenyl)hex-3-en-1-yne (IIc) (105 mg.), m. p. 184—186°, undepressed on admixture with the material obtained as above and exhibiting identical infrared absorption. No trace of the ketone (VI) was found.

Reaction of the Chloro-allene (Va) *with Sodamide in Liquid Ammonia.*—Ferric nitrate (20 mg.)

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and sodium (500 mg.) were added to liquid ammonia (200 ml.) at −35°; no blue colour remained after 0·5 hr. 1-Chloro-3,4-di-(*p*-benzoyloxyphenyl)hexa-1,2-diene (Va) (200 mg.) in dry ether (10 ml.) was added dropwise at −40°. After 0·5 hr., the usual working-up gave a dark brown oil which was phenolic, dissolving in 2N-sodium hydroxide, and was treated therein with benzoyl chloride (0·5 ml.) at 0°. Extraction with ether gave a yellow oil that was adsorbed on aluminium oxide (5 g.) from benzene. Elution with benzene–pentane (1 : 1; 2 × 10 ml.) gave a yellow oil (50 mg.), $\nu_{max.}$ 3250 (C≡CH), 1740 (OBz), 1650 cm.$^{-1}$ (C=C–C=O): insufficiency of material prevented further investigation. Elution with benzene and with ether gave a crystalline product thought to be 3,4-*di*-(p-*benzoyloxyphenyl*)*hex*-2-*enal* (VII), m. p. 192°, $\lambda_{max.}$ 232 mμ (ε 48,000), inflexion *ca.* 270 mμ (ε 17,100), $\nu_{max.}$ 1740 (OBz), 1650 (C=C–C=O) cm.$^{-1}$ [Found (after drying at 20°/1 mm. for 4 hr.): C, 78·1; H, 5·5. $C_{32}H_{26}O_5$ requires C, 78·35; H, 5·35%].

Hydrogenation of 3,4-*Di*-(p-*benzoyloxyphenyl*)*hex*-3-*en*-1-*yne* (IIc).—(*a*) Stilbœstrol dibenzoate (50 mg.), m. p. 216°, in ethyl acetate (100 ml.) was shaken in hydrogen with prereduced Adams catalyst (20 mg.) for 4 hr. Filtration from the catalyst and evaporation of the solvent gave a quantitative recovery of unchanged starting material.

(*b*) 3,4-Di-(*p*-benzoyloxyphenyl)hex-3-en-1-yne (IIc) (30 mg.) in ethyl acetate (50 ml.) was hydrogenated as above. The solid product was chromatographically purified on aluminium oxide (1 g.) prepared in benzene. Elution with benzene gave stilbœstrol dibenzoate, m. p. and mixed m. p. 216°, having the correct infrared spectrum.

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445. *Phosphine Oxide Complexes. Part IV.*[1] *Tetrahedral, Planar, and Binuclear Complexes of Copper(II) with Phosphine Oxides, and Some Arsine Oxide Analogues.*

By D. M. L. Goodgame and F. A. Cotton.

Some phosphine oxide complexes of copper(II) have been prepared, along with the arsine oxide analogues of two of them, and physical measurements made in order to determine the co-ordination symmetries. It appears that the co-ordination is tetrahedral in $[Cu(Ph_3PO)_2Cl_2]$ and $[Cu(Ph_3PO)_2Br_2]$, as in the analogous manganese(II), cobalt(II), and nickel(II) compounds. The triphenylarsine oxide analogues of these complexes do not seem to be tetrahedral. The complex cation $[Cu(Me_3PO)_4]^{2+}$ appears to be square, and the complex $CuCl_2,4(HO{\cdot}CH_2)_3PO$ also appears to contain tetragonally co-ordinated copper(II). The complex $Cu(CH_3{\cdot}CO_2)_2,Ph_3PO$ is very probably a carboxylate-bridged dimer.

The factors which determine the relative stabilities of the tetrahedral and planar configurations for four-co-ordinate complexes of manganese(II), cobalt(II), nickel(II), copper(II), zinc(II), and other ions are imperfectly understood. It is true that some contributing factors are recognized. For example, the effect of ligand field stabilization energies,[2] known in a semiquantitative way, would by itself probably lead to the following order of preference for the tetrahedral as compared with the planar configuration: Mn(II) ≈ Zn(II) > Co(II) > Cu(II) > Ni(II). Since other factors—steric effects, additional electrostatic forces, covalency in the metal–ligand bonds, and perhaps others—may be expected to vary more or less regularly with atomic number of the metal ion in a series of stoicheiometrically analogous complexes, it is not surprising that the above order is fairly consistent with observations although the latter are not extensive.

However, the predictive capabilities of present theory do not appear to extend much

[1] Part III, Bannister and Cotton, *J.*, 1960, 2276.
[2] George and McClure, *Progr. Inorg. Chem.*, 1959, **1**, 381.

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further. In particular, it is difficult to know exactly what properties of ligands, or what combination of properties, cause certain complexes of a given ion to be tetrahedral while others are planar. For example, with nickel(II), $[Ni(Ph_3P)_2Cl_2]$ is tetrahedral [3] while no other $[Ni(R_3P)_2Cl_2]$ complex has yet been prepared which is tetrahedral even when R is cyclohexyl.[4] Thus the steric factor alone does not seem decisive. It is probable, perhaps even likely, that a close balance of various factors determines the result so that simple predictive theory may remain beyond reach. In any event, the more experimental data which are available, the more likely it is that some general patterns may become evident. In this work, a very primitive and empirical hypothesis was tested. We have previously reported [5] the preparation of triphenylphosphine oxide complexes of nickel(II) halides, $[Ni(Ph_3PO)_2X_2]$ (X = Cl, Br, I), the bromide having also been reported by Issleib and Mitscherling,[6] and detailed evidence was presented to show that they are tetrahedral.[5] It has also been shown that the corresponding triphenylarsine oxide complexes containing chloride and bromide are tetrahedral,[7] and that the analogous triphenylphosphine oxide and triphenylarsine oxide complexes of manganese(II) are tetrahedral.[8] In view of the relative scarcity of tetrahedral nickel(II) complexes and, in particular, of the tendency of most other complexes of the type $[NiL_2X_2]$ to be planar, the hypothesis that triphenylphosphine oxide and its arsenic analogue might have an optimum set of properties favouring the tetrahedral configuration was considered. On this assumption, it seemed plausible that analogous copper(II) complexes might also be tetrahedral, since copper(II) should not be significantly more reluctant than nickel(II) to form tetrahedral complexes.

Few phosphine oxide or arsine oxide complexes of copper(II) have been reported before. Pebal [9] reported pale green $CuSO_4,3Et_3PO$; Pickard and Kenyon [10] reported light brown $CuCl_2,Et_3PO$; and Bannister and Cotton have reported $[Cu(Ph_3PO)_4](ClO_4)_2$ [11] and $[Cu(Ph_3PO)_2(NO_3)_2]$.[1] For the last two compounds the spectral data were explicitly interpreted as indicating square-planar configurations, and the colour of the sulphate complex leaves little doubt that it, too, has a planar or distorted octahedral configuration. The nature of the brown $CuCl_2,Et_3PO$ compound remains uncertain. Nyholm [12] has

TABLE 1. *Magnetic moments of the complexes.*

No.	Complex	Temp. (K)	$\chi^M_{corr.}$ ($\times 10^6$)	Diamagnetic corrn. ($\times 10^6$)	μ (B.M.) ($\pm 0{\cdot}02$)
1	$[Cu(Ph_3PO)_2Cl_2]$	299·1°	1797	405	2·08
2	$[Cu(Ph_3PO)_2Br_2]$	299·5	1664	426	2·01
3	$[Cu(Ph_3AsO)_2Cl_2]$	298·8	1539	449	1·92
4	$[Cu(Ph_3AsO)_2Br_2]$	300·7	993	470	1·56
5	$Cu(CH_3{\cdot}CO_2)_2,Ph_3PO$	299·2	959	246	1·52
6	$[Cu(Me_3PO)_4](ClO_4)_2$	298·4	1790	339	2·07 [a]
7	$CuCl_2,4(HO{\cdot}CH_2)_3PO$	297·8	1656	330	1·99

[a] Some indication of dependence of susceptibility on field strength.

reported the perchlorate and $[CuCl_2]^-$ salts of $[Cu(Ph_2MeAsO)_4]^{2+}$ which also appear to contain square-planar copper(II), as does [Cu(dimethyl-2-picolylarsine oxide)$_2$]$(ClO_4)_2$ reported by Goodwin and Lions.[13]

Knowledge of the behaviour and properties of tetrahedrally co-ordinated copper(II) is also limited. Golden-yellow cæsium tetrachlorocuprate(II) containing the tetrahedral

[3] Venanzi, *J.*, 1958, 719.
[4] Issleib and Brack, *Z. anorg. Chem.*, 1954, **277**, 258; Turco, Scatturin, and Giacometti, *Nature*, 1959, **183**, 601; Turco and Giacometti, *Ricerca sci.*, 1959, **29**, 1057.
[5] Cotton and Goodgame, *J. Amer. Chem. Soc.*, 1960, **82**, 5771.
[6] Issleib and Mitscherling, *Z. anorg. Chem.*, 1960, **304**, 73.
[7] Goodgame and Cotton, *J. Amer. Chem. Soc.*, 1960, **82**, 5774.
[8] Goodgame and Cotton, unpublished work.
[9] Pebal, *Annalen*, 1862, **120**, 202.
[10] Pickard and Kenyon, *J.*, 1906, **89**, 270.
[11] Bannister and Cotton, *J.*, 1960, 1878.
[12] Nyholm, *J.*, 1951, 1767.
[13] Goodwin and Lions, *J. Amer. Chem. Soc.*, 1959, **81**, 311.

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TABLE 2. *Electronic absorption spectra of the complexes.*

Compound	Medium	Colour	Absorption bands (mμ) (molar extinction coefficients for solutions)					
$[Cu(Ph_3PO)_2Cl_2]$	Solid	Yellow	345,	375,	425,			>1100
	10^{-3}M in $MeNO_2$	Yellow	~350sh,	380 (640),	470 (720),		900 (160)b	
$[Cu(Ph_3PO)_2Br_2]$	Solid	Dark red	Very strong absorption below 550 mμ					>1100
	10^{-3}M in $MeNO_2$	Green	~350sh,	372 (1970),	430 (1115),	643 (575),	910 (340)	
$[Cu(Ph_3AsO)_2Cl_2]$	Solid	Yellow-brown	345,		417, 480,	675,	~940	>1100
$[Cu(Ph_3AsO)_2Br_2]$	Solid	Olive-green	~360b		~440sh,	680,	~900sh	
$Cu(CH_3{\cdot}CO_2)_2,Ph_3PO$	Solid	Green	335,	~375sh,		750b		
	5×10^{-3}M in dioxan	Blue		374 (47),		659 (220)		
$[Cu(Me_3PO)_4](ClO_4)_2$	Solid	Pale blue				~600sh,	875b	
$CuCl_2,4(HO{\cdot}CH_2)_3PO$	Solid	Pale blue-green	325,	~380sh,			~845b	

sh = shoulder; b = broad.

tetrachlorocuprate(II) ion was the first compound in which its occurrence was definitely proved,[14] and other salts of tetrahedral $[CuCl_4]^{2-}$ with the same characteristic yellow colour have subsequently been reported.[15,16] The *X*-ray study of cæsium tetrachlorocuprate(II) revealed a significant flattening of the tetrahedron, and in cæsium tetrabromocuprate(II) the flattening is even greater.[17] These distortions have often been attributed to the Jahn–Teller effect, but according to Liehr [18b] spin–orbit coupling should produce a ground state which is not susceptible to a Jahn–Teller distortion. The purple compound $[Ph_3MeAs]_2[CuBr_4]$, has also been reported,[16] but no indication was given as to the configuration of the $[CuBr_4]^{2-}$ ion therein. Quite recently, Pappalardo [19] has studied the spectrum of copper(II) in the tetrahedral environment of the zinc oxide lattice.

Liehr [18] has published the complete theory (*i.e.*, including spin–orbit coupling) for the tetrahedrally co-ordinated copper(II) ion. As Pappalardo's paper [19] will show in detail, Liehr's results, together with the assumption that the Δ values in tetrahedral complexes will be ~4/9 of those (~11,000 $cm.^{-1}$) found in octahedral complexes, lead to the expectation that these complexes will have absorption bands in the region of 5000—7000 $cm.^{-1}$ but no absorption in the visible region due to *d–d* transitions. The reflectance spectrum of cæsium tetrachlorocuprate(II) [14] was indeed blank between 500 and 1000 mμ, the region where tetragonal and distorted octahedral copper(II) complexes normally absorb, and Pappalardo [19] has actually observed the absorption in ZnO:CuO at 5807 $cm.^{-1}$, in excellent agreement with theory. The yellow colour of the tetrachlorocuprate(II) ion is attributable to strong, presumably charge-transfer, absorption bands in the near ultraviolet region. Spectral data for solutions [14,16] of tetrachlorocuprate(II) and tetrabromocuprate(II) ions generally show some absorption in the red region, but this may be due to the instability of the tetrahedral configuration, leading to rearrangement or solvolytic decomposition in solution.

With regard to magnetic properties, Figgis [20] has shown that in a perfectly regular tetrahedral environment, copper(II) should have an effective moment of about 2·2 B.M.

[14] Helmholtz and Kruh, *J. Amer. Chem. Soc.*, 1952, **74**, 1176.
[15] Stürzer, *Z. Naturforsch.*, 1960, **15b**, 544.
[16] Gill and Nyholm, *J.*, 1959, 3997.
[17] Morosin and Lingafelter, *Acta Cryst.*, 1960, **13**, 807.
[18] (*a*) Liehr, *J. Phys. Chem.*, 1960, **64**, 43; (*b*) specifically, footnote 65.
[19] Pappalardo, Symp. Molecular Structure and Spectroscopy, Ohio State Univ., Columbus, Ohio, June 1960; we thank Dr. Pappalardo for a copy of his manuscript.
[20] Figgis, *Nature*, 1958, **182**, 1568.

However, it is well established by measurements in three laboratories [16,21] that μ_{eff} of copper(II) in cæsium tetrachlorocuprate(II) is only 1·96—2·00 B.M., and Gill and Nyholm [16] report values of 1·91 B.M. for $[Ph_3MeAs]_2[CuCl_4]$ and 1·96 B.M. for $[Ph_3MeAs]_2[CuBr_4]$. It is assumed that the distortions of these ions from regular tetrahedral symmetry cause quenching of some of the orbital contribution to the moment.

The new compounds prepared and characterized in this work are listed in Tables 1 and 2. Their magnetic moments show that they contain copper(II); the significance of the exact values will be considered presently. We shall discuss first compounds 1—4 since these are the ones expected to have tetrahedral configurations, as indicated earlier. For compounds 1 and 2 this appears definitely to be the case. These compounds are yellow and red, and, as shown in Table 2, they show no absorption in the red part of the visible spectrum in accord with the earlier theoretical and experimental results summarized above. Their magnetic moments are relatively high (Table 1), although not as high as predicted by theory for truly tetrahedral compounds. However, the fact that the presence of different kinds of ligand atoms, as well as possible distortions, will cause a decrease in the moment means that we may take the observed values as being in satisfactory accord with the presumption of a tetrahedral configuration in these two solid compounds.

TABLE 3. *Molar conductances of the complexes.*

Compound	Solvent	Temp. (c)	Molar conductance (mho) for 10^{-3}M-solution
$[Cu(Ph_3PO)_2Cl_2]$	$MeNO_2$	25·4°	19·8
$[Cu(Ph_3PO)_2Br_2]$	$PhNO_2$	25·8	10·2[a]
$[Cu(Me_3PO)_4](ClO_4)_2$	$MeNO_2$	23·1	201

[a] Colour of solid compound is dark red; colour of nitrobenzene solution is green.

Comparison of *X*-ray powder patterns of compounds 1 and 2 with those of their nickel(II), cobalt(II), and manganese(II) analogues, all of which seem definitely to be tetrahedral, has not provided any definite evidence concerning the configurations of the copper(II) compounds. Among the bromides, the nickel(II) and manganese(II) compounds are isomorphous, but the cobalt(II) and copper(II) compounds differ from the former two and from each other. Among the chlorides, the manganese(II) and cobalt(II) compounds are isomorphous and the pattern for the copper(II) compound is very similar but not quite identical. This may mean that the copper(II) compound is practically isomorphous but, as in other cases, slightly different because of a flattening of the tetrahedron. If this assumption is correct, then the *X*-ray data afford further evidence for the tetrahedral configuration in $[Cu(Ph_3PO)_2Cl_2]$ but provide no evidence either way in the case of $[Cu(Ph_3PO)_2Br_2]$.

Compounds 1 and 2 do not appear to be entirely stable in solution, even in the ionizing but relatively non-co-ordinating solvents, nitromethane and nitrobenzene. Their molar conductances in these solvents (Table 3) indicate that they are probably non-ionic as solids, as indicated by the manner in which we write their formulæ, but that some solvolytic dissociation does occur. In nitromethane and nitrobenzene, a true 1 : 1 electrolyte would have molar conductances in the ranges 80—100 and 20—30 ohm^{-1} respectively. $[Cu(Ph_3PO)_2Cl_2]$ gives a yellow solution in nitromethane with a spectrum that differs little from the reflectance spectrum of the solid, suggesting that the molecule retains its tetrahedral configuration in this solution. For $[Cu(Ph_3PO)_2Br_2]$ there is evidently considerable, if not total, loss of the tetrahedral configuration upon dissolution in nitromethane, since the red solid gives a green solution the spectrum of which shows prominent absorption bands at 643 and 910 mμ. For the chloride complex, yellow solutions were obtained in certain other solvents as well, *e.g.*, acetonitrile, acetone, ethyl acetate, benzene, toluene, and chlorobenzene, although alcohols gave green solutions. For the bromide complex, however, green solutions were obtained in all solvents used. Evidently the

[21] Figgis and Harris, *J.*, 1955, 855; M. D. Meyers (M.I.T., 1957), unpublished results.

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stability of the tetrahedral configuration in the bromide complex is very low, while for the chloride complex it is much higher.

For the arsine oxide complexes, $[Cu(Ph_3AsO)_2Cl_2]$ and $[Cu(Ph_3AsO)_2Br_2]$, the existence of the tetrahedral configuration is unlikely, especially for the latter. Both of these compounds show absorption in the red part of the spectrum in their reflectance spectra, and for the bromide complex the 680 mμ band appears to be quite strong. Both of these compounds were virtually insoluble in all common solvents tested, so that no investigations of their properties in solution were possible. The magnetic moment of $[Cu(Ph_3AsO)_2Cl_2]$,

TABLE 4. *Infrared absorption spectra.*

	P–O stretching frequency ($cm.^{-1}$)	Shift ($cm.^{-1}$)
Ph_3PO [27]	1195	—
$[Cu(Ph_3PO)_2Cl_2]$	1142	−53
$[Cu(Ph_3PO)_2Br_2]$	1145, 1169	−38 (av)
$Cu(OAc)_2,Ph_3PO$	1168	−27
Me_3PO [27]	1174	—
$[Cu(Me_3PO)_4](ClO_4)_2$	$\leqslant$1125	$\geqslant$−49

	As–O stretching frequency ($cm.^{-1}$)	Shift ($cm.^{-1}$)
Ph_3AsO	880	—
$[Cu(Ph_3AsO)_2Cl_2]$	840	−40
$[Cu(Ph_3AsO)_2Br_2]$	842	−38

Data concerning anions:	Absorption maxima ($cm.^{-1}$)
$[Cu(Me_3PO)_4](ClO_4)_2$	1085 vs. (broad)
Ionic perchlorates [29]	1050—1150vs
$Cu(OAc)_2,Ph_3PO$	1630s, 1435s
$Cu(OAc)_2,H_2O$ [25]	1603 1418

1·92 B.M., would be equally consistent with a planar or a distorted tetrahedral configuration. The reason for the low moment, 1·56 B.M., of $[Cu(Ph_3AsO)_2Br_2]$ is not known. The measurement was repeated several times on a specimen giving a good analysis.

With cupric acetate, triphenylphosphine oxide gives the 1 : 1 complex $Cu(OAc)_2,Ph_3PO$. The spectral data indicate the presence of octahedrally or tetragonally co-ordinated copper(II), and the low magnetic moment, 1·52 B.M., makes it likely that this compound is a dimer, closely related structurally to the previously known dimers of carboxylic acid salts of copper(II), in which the four $R{\cdot}CO_2$ groups form CuOC(R)OCu bridges, with a neutral ligand also co-ordinated to each copper ion.[22,23] Further support for this structure is provided by the appearance of an absorption band ~375 mμ; it appears that such a band is diagnostic for the carboxylate-bridged structure.[23,24] The infrared spectrum also supports the dimeric structure when the positions of the symmetric and the asymmetric carboxylate stretching frequencies (Table 4) are compared to the results of Nakamoto *et al.*[25] It has recently been shown that $[Cu(OAc)_2,C_5H_5N]_2$ has the carboxylate-bridged structure.[26] Evidently, a variety of neutral ligands may occur in this type of structure.

The green-blue complex, $CuCl_2,4(HO{\cdot}CH_2)_3PO$, appears definitely to contain tetragonally co-ordinated copper. Its magnetic moment is consistent with this, while the appearance of a broad asymmetric absorption band with a peak at ~845 mμ provides strong positive evidence. Its insolubility in suitable solvents prevented measurements of molecular weight or electrolytic conductance.

Tetrakis(trimethylphosphine oxide)copper(II) perchlorate was prepared for comparison with the triphenylphosphine oxide analogue previously reported [11] and shown to have an essentially planar CuO_4 grouping with non-linear Cu–O–P chains. In the methyl compound reported here, planarity of the CuO_4 grouping is possible even with little or no bending of the Cu–O–P chains, and the similarity of the spectral and magnetic properties of the copper(II) ions in the two compounds supports the belief that the copper(II) is tetragonally co-ordinated in both.

[22] van Niekerk and Schoening, *Acta Cryst.*, 1953, **6**, 227.
[23] Martin and Whitley, *J.*, 1958, 1394.
[24] Tsuchida and Yamada, *Nature*, 1955, **176**, 1171; Tsuchida, Yamada, and Nakamura, *ibid.*, 1956, **178**, 1192.
[25] Nakamoto, Fujita, Tanaka, and Kobayashi, *J. Amer. Chem. Soc.*, 1957, **79**, 4904.
[26] Hanic, Štempelová, and Hanicová, Abs. Supplementary Papers, Fifth Internat. Congr. I.U.C., Cambridge, August, 1960.

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Infrared spectra of all compounds were recorded in the rock-salt region and some of the more significant bands are listed in Table 4. It has previously been shown [27,28] that formation of a dative bond from the oxygen atom of an R_3PO or X_3PO molecule to a metal ion causes a significant lowering of the frequency of the infrared band due principally to P–O stretching. As Table 4 shows, the three triphenylphosphine oxide complexes reported here show this effect clearly. A similar effect would be expected for arsine oxide complexes and has been observed. By comparison of the spectra of triphenylarsine and triphenylarsine oxide, it seems evident that the As–O stretching frequency is 880 cm.$^{-1}$. In the two arsine oxide complexes reported here the position of this band is ~40 cm.$^{-1}$ lower.

In $[Cu(Me_3PO)_4](ClO_4)_2$ the P–O band is difficult to identify because the heavy absorption by perchlorate ion obscures the region in which it is expected. We can thus only place an upper limit of ~1125 cm.$^{-1}$ on its frequency. The infrared spectra of tris(hydroxymethyl)phosphine oxide and $CuCl_2,4(HO{\cdot}CH_2)_3PO$ are not easy to interpret with certainty, and the data are not therefore recorded in Table 4. It is not unlikely, however, that broad bands at 1137 cm.$^{-1}$ in tris(hydroxymethyl)phosphine oxide and at 1106 cm.$^{-1}$ in the complex are due to P–O stretching.

In summary, it may be said that the tendency of complexes of the type $[M(Ph_3PO)_2X_2]$, where X is a halogen, to be tetrahedral is observed when M = Cu(II) as well as when M = Ni(II),[6] Co(II),[30] and Mn(II),[8] but that on replacement of triphenylphosphine oxide with triphenylarsine oxide the tetrahedral configuration appears to be lost in the case of copper(II).

Experimental

Trimethylphosphine Oxide and Triphenylarsine Oxide.—These compounds were prepared by methods reported in the literature.[27,31]

Dichlorobis(triphenylphosphine Oxide)copper(II).—A solution of triphenylphosphine oxide (4·88 g., 0·0176 mole) and cupric chloride dihydrate (1·36 g., 0·008 mole) in absolute ethanol (29 ml.) was evaporated, in a partial vacuum over sulphuric acid, until clusters of pale yellow crystals were formed. These were filtered off, washed with a small quantity of cold absolute ethanol, and dried *in vacuo* over sulphuric acid (yield 85%) (Found: C, 62·4; H, 4·5; Cu, 9·2; P, 9·2. $C_{36}H_{30}Cl_2CuO_2P_2$ requires C, 62·6; H, 4·4; Cu, 9·2; P, 9·0%). The *compound* recrystallized from ethyl methyl ketone (3 g. in 17 ml.). It was soluble to form yellow solutions in nitromethane, acetonitrile, or acetone, and also in hot benzene, toluene, chlorobenzene, or ethyl acetate. Green solutions were formed with alcohols, suggesting dissociation and/or rearrangement of the complex. The complex was insoluble in chloroform, carbon tetrachloride, cyclohexane, and light petroleum. When the compound was moistened with absolute ethanol and exposed to the atmosphere it became green-blue on the exposed surface, presumably owing to hydration since the blue colour reverted to yellow in a desiccator. The compound melted at 176° to a dark red melt, which reverted to a yellow solid on cooling.

Dibromobis(triphenylphosphine Oxide)copper(II).—This compound was prepared by the procedure used for the corresponding chloro-complex. The crude, brown product was triturated with ether (2 × 25 ml.) and then recrystallized from ethyl acetate (5·2 g. in 225 ml.). Dark red needles were obtained which were washed first with ethyl acetate, then with dry ether, and dried *in vacuo* (yield 24%); they had m. p. 159·5° (Found: C, 55·4; H, 3·8; Cu, 8·2; P, 8·1. $C_{36}H_{30}Br_2CuO_2P_2$ requires C, 55·4; H, 3·9; Cu, 8·15; P, 7·9%). The *compound* was soluble to form green solutions in acetone, ethyl methyl ketone, acetonitrile, nitromethane, dimethylformamide, dioxan, or propan-2-ol, and in hot benzene and chlorobenzene. It was insoluble in carbon tetrachloride, cyclohexane, and light petroleum and decomposed in chloroform. The complex readily dissolved in alcohols to form yellow or brown solutions.

[27] Cotton, Barnes, and Bannister, *J.*, 1960, 2199.
[28] Sheldon and Tyree, *J. Amer. Chem. Soc.*, 1958, **80**, 4775.
[29] Miller and Wilkins, *Analyt. Chem.*, 1952, **24**, 1253.
[30] Holm and Cotton, *J. Chem. Phys.*, 1960, **32**, 1168.
[31] Shriner and Wolf, *Org. Synth.*, 1950, **30**, 97.

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Diacetato(triphenylphosphine Oxide)copper(II).—A solution of triphenylphosphine oxide (4·59 g., 0·0165 mole) and cupric acetate monohydrate (1·5 g., 0·0075 mole) in absolute ethanol (85 ml.) yielded green crystals in ~18 hr. The *product* was filtered off, washed with absolute ethanol, and dried *in vacuo* over phosphorus pentoxide (yield 77%), m. p. 238° (Found: C, 56·9; H, 4·7; Cu, 13·85; P, 6·9. $C_{22}H_{21}CuO_5P$ requires C, 57·45; H, 4·6; Cu, 13·8; P, 6·7%). The compound was initially soluble in methylene chloride and in chloroform giving blue solutions, but these rapidly became opalescent with decomposition of the complex. Green solutions were formed in the lower alcohols, but the compound was found to be little soluble in most organic solvents.

Tetrakis(trimethylphosphine Oxide)copper(II) *Perchlorate*.—A solution of trimethylphosphine oxide (2·46 g., 0·027 mole) in hot absolute ethanol (15 ml.) was added to one of cupric perchlorate (2·47 g., 0·0067 mole) also in hot absolute ethanol (10 ml.). The pale blue solid which immediately formed was collected and recrystallized from absolute ethanol (3·35 g. in 150 ml.). The pale blue *product* obtained was filtered off, washed with ethanol and dried, in a drying-pistol, *in vacuo* over phosphorus pentoxide at about 70° (yield 56%; m. p. 240° (Found: C, 22·7; H, 5·7; Cl, 11·0; Cu, 10·0; P, 19·4. $C_{12}H_{36}Cl_2CuO_{12}P_4$ requires C, 22·85; H, 5·75; Cl, 11·2; Cu, 10·1; P, 19·65%). The complex formed blue solutions in water, methanol, nitromethane, acetonitrile, and hot ethanol, but was insoluble in methylene chloride, chloroform, acetone, dioxan, and toluene.

Dichlorotetrakis(trishydroxymethylphosphine Oxide)copper(II).—On cooling a hot solution of trishydroxymethylphosphine oxide (4·2 g., 0·03 mole) and cupric chloride dihydrate (2·56 g., 0·015 mole) in n-butanol (90 ml.) long, very pale, green-blue needles were formed. These were filtered off, washed first with n-butanol, then absolute ethanol and dried *in vacuo* over phosphorus pentoxide (yield 74%, based on phosphine oxide; m. p. 126°) (Found: C, 21·5; H, 5·3; Cu, 9·1; P, 18·15. $C_{12}H_{36}Cl_2CuO_{16}P_4$ requires C, 20·7; H, 5·2; Cu, 9·1; P, 17·8%). The *compound* was soluble in water and somewhat soluble in the lower alcohols, but insoluble in all other common solvents tried.

Complex of Cupric Bromide with Trishydroxymethylphosphine Oxide.—A pale blue-green crystalline complex of trishydroxymethylphosphine oxide with cupric bromide was obtained by a method analogous to that used for the chloro-complex. However analyses were unsatisfactory and the compound decomposed in a few days after isolation.

Dichlorobis(triphenylarsine Oxide)copper(II).—A solution of triphenylarsine oxide (3·22 g., 0·01 mole) in absolute ethanol (14 ml.) was added to one of cupric chloride dihydrate (0·86 g., 0·005 mole) also in absolute ethanol (6 ml.). The yellow solid which was immediately formed was filtered off and recrystallized, first, from absolute ethanol and then from chlorobenzene. The yellow-brown product was washed with chlorobenzene, then benzene and dried *in vacuo* (yield 37%; m. p. 187°) (Found: C, 55·8; H, 3·9; As, 19·0. $C_{36}H_{30}As_2Cl_2CuO_2$ requires C, 55·5; H, 3·9; As, 19·2%). The *compound* was soluble to form greenish-yellow solutions in methylene chloride, chloroform, and dimethylformamide and in hot alcohols and chlorobenzene. It was insoluble in all other common solvents.

Dibromobis(triphenylarsine Oxide)copper(II).—This dark olive-green *complex* was prepared analogously to the chloro-complex in 73% yield, with m. p. 241° (Found: C, 50·6; H, 3·5; As, 17·45; Cu, 7·6. $C_{36}H_{30}As_2Br_2CuO_2$ requires C, 49·8; H, 3·5; As, 17·3; Cu, 7·3%). When first filtered from the ethanolic reaction mixture the compound was dark purple but changed to dark olive-green on drying. Attempts to obtain a dry, purple form of the compound were unsuccessful. The compound was soluble in hot alcohols, chlorobenzene, ethyl methyl ketone, and dimethylformamide, but insoluble in other organic solvents.

Electrolytic Conductance Measurements.—These were made with a Serfass bridge and a conventional cell, previously calibrated with aqueous potassium chloride. The results are shown in Table 3. The remaining complexes were too insoluble in, or were decomposed by, nitrobenzene and nitromethane.

Magnetic Measurements.—Magnetic-susceptibility measurements were made at room temperature by the Gouy method as previously described.[30] Mohr's salt and copper sulphate pentahydrate were used to calibrate the Gouy tube. Duplicate determinations were carried out for each compound, over a range of field strengths. The diamagnetic corrections were calculated by using Pascal's constants and previously reported values for the phosphine and arsine oxides.[11,33] The results are shown in Table 1.

[33] Foex, "Constants Selectionées Diamagnetisme et Paramagnetisme," Masson et Cie., Paris, 1957.

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Infrared Absorption Spectra.—These were obtained with a Perkin-Elmer model 21 spectrophotometer, fitted with a rock-salt prism. Nujol mulls were used. The relevant data from the spectra are shown in Table 4, together with reference data from the literature.

Electronic Spectra.—The reflectance spectra of the solid compounds were measured by using a Beckman DU spectrophotometer with the standard Beckman reflectance accessory and magnesium carbonate as the reference sample. The solution spectra of the compounds $[Cu(Ph_3PO)_2Br_2]$ and $Cu(CH_3{\cdot}CO_2)_2,Ph_3PO$ were obtained with a Cary 11MS recording spectrophotometer; the solution spectrum of $[Cu(Ph_3PO)_2Cl_2]$ was obtained with a Beckman DU spectrophotometer. The results are shown in Table 2.

X-*Ray Powder Diagrams.*—These were obtained for us by Miss R. Babineau of Arthur D. Little Co., to whom we express our appreciation.

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446. *The Hydrolysis of Acetic Anhydride. Part VI.* Kinetics in Deuterium Oxide Solution.*

By A. R. Butler and V. Gold.

The velocities of the " spontaneous " and acetate-catalysed hydrolyses of acetic anhydride are reduced (by factors of 2·9 and ~1·7, respectively) on changing from ordinary water to deuterium oxide as solvent. The formate-catalysed reaction is only slightly affected by this change of solvent. A reaction mechanism is put forward which accommodates the isotope effects and, at the same time, provides an explanation of the catalytic effect of acetate ions in this reaction. The rate-controlling step in this mechanism is a proton-transfer from hydrogen ion or acetic acid to the oxygen atom of an anionic intermediate. The general admissibility of a rate-determining step of this kind in a measurably slow reaction is discussed.

The small but definite catalytic effect of acetate ions on the hydrolysis of acetic anhydride [1] has never been satisfactorily explained. It is possible that it is really the manifestation of a more general catalytic effect of bases. However, with tertiary amines [2] or carboxylate ions [1] (except acetate ions) other catalytic or anti-catalytic phenomena supervene, and these have so far prevented the detection (or proof of the absence) of the suspected general base-catalysis. As a rough rule, the carboxylate ions derived from acids that are stronger than acetic acid appear to be catalysts by virtue of the formation of a more easily hydrolysed unsymmetrical anhydride,[1,3] *e.g.*, acetic formic anhydride, whereas the addition of, for example, propionate ions retards the hydrolysis owing to the formation of the less reactive acetic propionic anhydride.[1,4] No such effect complicates the catalysis of an anhydride by its own carboxylate ions. Since no credible transition state could be formulated by rearrangement of the parts of acetic anhydride and acetate, it was considered that comparative measurements in ordinary and heavy water as solvents might throw some light of the degree of involvement of water in the transition state of the acetate-catalysed and also of the " spontaneous " reaction. In other spontaneous solvolytic hydrolyses, *e.g.*, of alkyl halides and alkyl sulphonates, the formation of the transition state from water and the substrate alone does not give rise to a large kinetic solvent isotope-effect.[5] The

* Part V, *J.*, 1955, 843.

[1] Kilpatrick, *J. Amer. Chem. Soc.*, 1928, **50**, 2891.
[2] Leman, *Bull. Soc. chim. France*, 1945, **12**, 908; 1947, **14**, 514; Bafna and Gold, *J.*, 1953, 1406; Gold and Jefferson, *J.*, 1953, 1409.
[3] Gold and Jefferson, *J.*, 1953, 1416.
[4] Kilpatrick and Kilpatrick, *J. Amer. Chem. Soc.*, 1930, **52**, 1418.
[5] Robertson and Laughton, *Canad. J. Chem.*, 1957, **35**, 1319.

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detection of an appreciable solvent isotope-effect in the present case would therefore indicate a substantial difference in transition-state structure from that applying to nucleophilic substitution by water at a saturated carbon atom. These expectations have now been realised by experiment, and the interpretation of the size of the observed isotope effects has led to the formulation of a mechanism for the acetate catalysis.

Experimental

Deuterium oxide was the Norsk Hydro product with a stated deuterium content of >99%, and all the results quoted for heavy water relate to isotopic compositions in the range 99·5—99·8%.

Acetic anhydride was purified as described by Gold and Hilton.[6]

Sodium acetate (" AnalaR," anhydrous) and sodium chloride (" AnalaR ") were dried at 110° for several hours and allowed to cool in a vacuum-desiccator. Sodium formate was dried *in vacuo* for several days and its purity was checked by analysis.[7]

Dioxan (" AnalaR ") was refluxed over sodium until the metal surface stayed bright, and then fractionally distilled. Mixtures of dioxan with ordinary and with heavy water were made up by diluting a measured or weighed amount of water to a fixed total volume with dioxan.

Solutions of acetic acid in heavy water were prepared by hydrolysis of acetic anhydride; those of formic acid were made by addition of anhydrous (isotopically normal) acid (" AnalaR "). At an acid concentration of 0·03M, the concentration of protium introduced thereby into the heavy water is insignificant.

In kinetic experiments (at 25°) the concentration of undecomposed acetic anhydride in solution (initial concentration *ca.* 10^{-3}M) was followed as a function of time by a spectrophotometric technique developed from Lees and Saville's colorimetric method.[8] This procedure gave results in agreement with runs followed by Vles's aniline–water method.[9] In order to help rapid dissolution of acetic anhydride, reaction mixtures were prepared by adding *ca.* 0·05 ml. of a stock solution of acetic anhydride in acetone to 10 ml. of water or aqueous buffer solution. The reported rate constants therefore relate to a solvent mixture containing *ca.* 0·5% of acetone by volume.

First-order rate constants are expressed in the units sec.$^{-1}$, and second-order constants as l. sec.$^{-1}$ mole^{-1}. In accordance with usual practice, the spontaneous rates are reported as first-order rate constants, k_0 (*i.e.*, without introducing the molarity of water into the calculation). Observed first-order rate constants in the presence of added substances are designated by the symbol k_1. All runs were strictly of first-order. The isotopic nature of the solvent is indicated by the superscripts H and D.

Results

Spontaneous Rate.—The results are given in Tables.

(a) *Spontaneous rate constants in ordinary water* (k_0^H).
$2·59 \times 10^{-3}$, $2·61 \times 10^{-3}$, $2·63 \times 10^{-3}$. Mean: $2·61 \times 10^{-3}$.

(b) *Spontaneous rate constants in deuterium oxide* (k_0^D).
$8·94 \times 10^{-4}$, $8·97 \times 10^{-4}$, $8·97 \times 10^{-4}$. Mean: $8·96 \times 10^{-4}$.

Isotope effect: $k_0^H/k_0^D = 2·9$.

(c) *Spontaneous rate in dioxan–water mixtures.*

Molarity of water (H_2O)	$10^5k_0^H$	Molarity of water (H_2O)	$10^5k_0^H$	Molarity of water (D_2O)	$10^5k_0^D$	$10^5k_0^H$ *	k_0^H/k_0^D
49·4	172	25·9	13·4	50·1	71	180	2·5
44·1	111	22·0	7·91	42·1	38·4	92	2·4
38·3	59·5	17·6	3·63	34·5	19·5	40	2·1
33·5	41·1	14·2	2·54	25·5	5·22	12·7	2·4
27·7	21·2			23·5	3·84	9·7	2·5
				16·0	1·86	3·3	1·8

* Calc. for the corresponding molarity of ordinary water by interpolation from the experimental rate constants in solvent mixtures with ordinary water.

[6] Gold and Hilton, *J.*, 1955, 838.
[7] Kolthoff and Belcher, " Volumetric Analysis," Interscience Publ. Inc., New York, 1957, Vol. III, p. 567.
[8] Lees and Saville, *J.*, 1958, 2262.
[9] Vles, *Rec. Trav. chim.*, 1933, **52**, 809.

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Effect of Added Sodium Chloride.—This effect is also illustrated in Tables.

(a) *Added sodium chloride in ordinary water.*

[NaCl] (M)	—	0·149	0·299	0·397	0·504	0·598
10^3k_1	2·61	2·54	2·45	2·37	2·30	2·25
10^3k_1 (calc.*)	2·61	2·52	2·43	2·37	2·31	2·25

* Calc. from the empirical expression $10^3k_1 = 2·61 - 0·60$[NaCl].

(b) *Added sodium chloride in heavy water.*

[NaCl] (M)	—	0·443	0·675
10^4k_1	8·96	8·83	8·63
10^4k_1 (calc.*)	8·96	8·78	8·69

* Calc. from expression $10^4k_1 = 8·96 - 0·40$[NaCl].

Effect of Added Acetic Acid.—This is illustrated by the following results:

[AcOH]	0	0·021	0·031	0·041	0·0875	0·103	0·157	0·205
$10^3k_1^H$	2·61	2·63	2·54	2·49	2·42	2·36	2·21	2·10

The small increase in rate at low concentrations of acetic acid was observed in a number of independent experiments and is considered to be real.

Acetate Catalysis.—In order to avoid complications from the non-linear effect of added acetic acid (whatever its cause), the acetate catalysis was studied in buffer solutions containing a fairly high concentration (~0·1M) of acetic acid. (This may be done without introducing any significant catalytic effect of hydrogen ions.) The rate increase accompanying the addition of sodium acetate was then found (see Tables) to be proportional to the acetate concentration.

(a) *Added acetic acid and sodium acetate in ordinary water.* [AcOH] = 0·0875M.

[NaOAc] (M)	0	0·031	0·061	0·091	0·120	0·181
10^3k_1	2·42	2·53	2·69	2·78	2·94	3·10
10^3k_1 (calc.*)	2·42	2·54	2·66	2·78	2·90	3·14

* Calc. from expression $10^3k_1 = 2·42 + 4·0$[NaOAc].

(b) *Added acetic acid and sodium acetate in heavy water.* [AcOH] ~ 0·08M.

[NaOAc] (M)	0	0·103	0·143
10^3k_1	0·88	1·16	1·25
10^3k_1 (calc.*)	0·88	1·15	1·26

* Calc. from expression $10^3k_1 = 0·88 + 2·6_5$[NaOAc].

Kilpatrick [1] has suggested that the electrolyte effect, which must be presumed to be one of the consequences of the addition of sodium acetate, can be estimated from experiments with sodium chloride [1] so that a corrected catalytic coefficient (k_{OAc}) can be calculated as $k_{OAc} = k_{NaOAc} - k_{NaCl}$, where k_X is the observed coefficient of the concentration of X in the empirical expressions for the variation of k_1 with [X], given as footnotes to the respective Tables above.

On this basis,

$$k^H_{OAc} = (4·0 + 0·60) \times 10^{-3} = 4·6 \times 10^{-3},$$

and

$$k^D_{OAc} = (2·6_5 + 0·04) \times 10^{-3} = 2·7 \times 10^{-3},$$

whence

$$k^H_{OAc}/k^D_{OAc} = 1·7.$$

Without consideration of the electrolyte effect, the solvent isotope-effect for acetate catalysis would be given by:

$$k^H_{NaOAc}/k^D_{NaOAc} = 4·0 \times 10^{-3}/2·6_5 \times 10^{-3} = 1·5.$$

The value 1·7 is the more significant ratio, although the relatively great importance of the general electrolyte effect complicates the situation.

Formate Catalysis.—Sodium formate has a much greater effect on the reaction velocity than sodium acetate and, accordingly, the complicating features discussed above for the determination of the catalytic coefficient of the acetate ion are absent. The results are again tabulated.

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(a) *Added formate in ordinary water.* $[H{\cdot}CO_2Na] \sim 0{\cdot}045$M.

$100[H{\cdot}CO_2Na]$ (M)	—	0·96	1·92	2·88	3·66	4·54
10^3k_1	2·79	3·59	4·15	5·03	5·51	6·40
10^3k_1 (calc.*)	2·79	3·53	4·27	5·01	5·61	6·28

* Calc. from expression $10^3k_1 = 2{\cdot}79 + 77[H{\cdot}CO_2Na]$.

(b) *Added formate in heavy water.* $[H{\cdot}CO_2D] \approx 0{\cdot}035$M.

$[H{\cdot}CO_2Na]$ (M)	—	0·0325
10^3k_1	1·06	3·43, 3·38
$k^D_{H{\cdot}CO_2Na}$	—	73, 71

As the electrolyte effect is negligible compared with the catalytic acceleration,

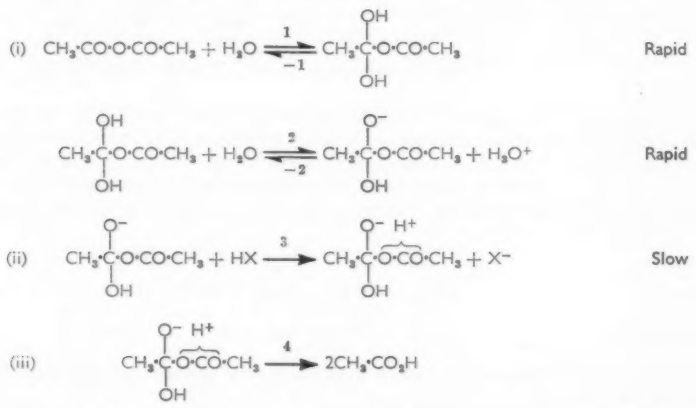
$$k^H_{H{\cdot}CO_2Na}/k^D_{H{\cdot}CO_2Na} = k^H_{H{\cdot}CO_2^-}/k^D_{H{\cdot}CO_2^-}$$
$$= 77 \times 10^{-3}/72 \times 10^{-3} = 1{\cdot}0_7.$$

Discussion

The salient results are these: In aqueous solutions at 25°, the velocities of hydrolysis are reduced when the ordinary water of the solvent is replaced by deuterium oxide. The effect is most marked for the spontaneous rate, for which there is a reduction by a factor of 2·9. The corresponding factor for the catalytic coefficient of acetate ions is *ca.* 1·7, and that for formate ions is 1·1. In mixtures of dioxan with ordinary and with heavy water, the solvent isotope-effect of the spontaneous rate falls off gradually, and apparently not quite regularly, with increasing dioxan content of the media.

The small solvent isotope-effect found in the formate catalysis is of the order of magnitude commonly observed for reactions in which O–H bonds of the solvent are not ruptured in the rate-controlling step.[5] This result does not disturb the view [3] that the formation of acetic formic anhydride is the rate-controlling step in formate catalysis.*

The large solvent isotope-effects in the cases of the other two reactions indicate that their mechanism involves a weakening of O–H bonds on formation of the transition state,



and a mechanism differing appreciably from a simple S_N2 substitution. The following mechanism takes account of Bender's conclusions [10] concerning the importance of hydration of the carbonyl group in the course of ester hydrolysis and also of the detailed information, obtained in the main by R. P. Bell and his school, regarding the thermodynamics and kinetics of the hydration of the carbonyl group in acetaldehyde. The scheme appears to

* Owing to a misprint, a conclusion that Gold and Jefferson's results were " not incompatible " with the suggestion made by Kilpatrick was erroneously printed in ref. 3 as " not compatible."

[10] Bender, *Chem. Rev.*, 1960, **60**, 63.

account for the isotope effects and, at the same time, appears to give an adequate explanation of the occurrence of acetate catalysis.

The mechanism postulates (i) the formation of an anionic species from hydroxide ion and acetic anhydride in a pre-equilibrium, and (ii) the rate-controlling reaction (3) of this anion with an acid. In detail, these steps can be represented as shown. It is assumed that there is no significant accumulation of any of the intermediates. The dissection of the pre-equilibrium (i) into the two steps shown is arbitrary and was done for reasons of thermodynamic convenience which will become obvious; it would have been equally justifiable to represent this reaction as the addition of hydroxide ions to acetic anhydride, the hydroxide ions having been formed by the rapid autoprotolysis of the solvent, or in some other way. Steps following the rate-controlling proton transfer (3) are considered to be kinetically insignificant, *i.e.*, reaction (4) is faster than the reversal of (3). HX represents a general Brønsted acid. Two cases of interest are (*a*) $HX = H_3O^+$ and (*b*) $HX = CH_3{\cdot}CO_2H$, and these give rise to the following equations:

$$(a)\ v = K_1K_2k_3^{H_3O^+}[Ac_2O].$$

This corresponds to the " uncatalysed " or " spontaneous " reaction with a first-order rate constant

$$k_0 = K_1K_2k_3^{H_3O^+}. \qquad (1)$$

$$(b)\ v = K_1K_2k_3^{AcOH} \cdot \frac{[AcOH]}{[H_3O^+]} \cdot [Ac_2O]$$

$$= K_1K_2\frac{k_3^{AcOH}}{K_{AcOH}}[OAc^-][Ac_2O],$$

where K_{AcOH} is the acid dissociation constant of acetic acid. This case represents the acetate-catalysed reaction, and the catalytic coefficient is given by

$$k_{OAc^-} = K_1K_2k_3^{AcOH}/K_{AcOH}. \qquad (2)$$

The rate-controlling step (3) in our scheme is a proton transfer from the conjugate acid of the catalyst to an (unspecified) oxygen atom of the anionic intermediate. The scheme conflicts with a widely accepted principle of solution kinetics. It has, for example, been stated by Bell and Darwent [11] that acid–base reactions involving the transfer of a proton to or from an oxygen atom are known to be very rapid and cannot, therefore, be rate-determining in the reaction mechanism of a catalysed reaction. However, this conclusion is not necessarily correct. While it is true that the *rate constants* of such processes will have large values it does not follow that the processes themselves must be rapid. In our case the reaction velocity will be the product of the rate constant *and of the concentration of the intermediate*. Provided the intermediate is present in very low concentration, a rate-determining step with a very large rate constant may still produce a measurable velocity. This proviso will hold in the present example.

There are, of course, no direct measurements on the postulated pre-equilibrium (i) for acetic anhydride from which the concentration of the intermediate anion could be calculated. The value of the corresponding equilibrium constant (K_1) is, however, known for the addition of hydroxide ion to acetaldehyde in aqueous solution. In this case K_1 lies [12,13] between 1 and 2 and [14] $K_2 = 3{\cdot}3 \times 10^{-14}$ (the concentration of water being set equal to unity), so that $K_1 = K_1K_2 \simeq 5 \times 10^{-14}$ (see also ref. 15). The value of this

[11] Bell and Darwent, *Trans. Faraday Soc.*, 1950, **46**, 34.
[12] Bell and Clunie, *Trans. Faraday Soc.*, 1952, **48**, 439; Bell and Rand, *Bull. Soc. chim. France*, 1955, 115.
[13] Rumpf and Bloch, *Compt. rend.*, 1951, **233**, 1364; Lombardi and Sogo, *J. Chem. Phys.*, 1960, **32**, 635.
[14] Bell and McTigue, *J.*, 1960, 2983.
[15] Rumpf, *Bull. Soc. chim. France*, 1946, **13**, 546; 1955, 117.

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constant for acetic anhydride may well be somewhat greater, but it is not expected to differ from the acetaldehyde value by many powers of ten. On the basis of considerations put forward by Bell *et al.*,[12] K_1 should be somewhat smaller and (by straightforward analogies) K_2 greater than the values for acetaldehyde. If, for the sake of illustration only, a value of $K_1 \approx 10^{-12}$ is taken to apply to acetic anhydride, and we combine this with the experimental rate constant of the spontaneous reaction at 25°, we obtain a value of 2×10^9 for $k_3^{H_3O^+}$. This is clearly a very large rate constant and only about ten times smaller than the value for a diffusion-controlled bimolecular reaction in solution.[16] If K_1 were 5×10^{-14}, $k_3^{H_3O^+}$ would roughly equal the rate constant for a diffusion-controlled reaction. The above scheme cannot, therefore, be rejected on the ground that the required rate constant of the rate-controlling step has too *small* a value for a proton-transfer of this type.

The fact that the spontaneous hydration of acetaldehyde is a measurably slow process [11,12] need not conflict with the requirement that the pre-equilibrium (i) must be rapidly established for the hydrolysis of acetic anhydride. It is difficult to predict whether the rate of formation of the dihydroxy-intermediate would be much greater in the case of acetic anhydride, but the problem may not be relevant to the present issue since the anionic intermediate is not necessarily formed *via* the dihydroxy-compound, but could result from the interaction of acetic anhydride and hydroxide ion.

In order to discuss the solvent isotope-effects we must consider how the factors into which k_0 and k_{OAc} can be split [see equations (1) and (2)] would be altered on passing from ordinary to heavy water as solvent. By analogy with the hydration equilibrium for acetaldehyde,[17] K_1^H/K_1^D should have a value not far removed from unity. The ratio K_2^H/K_2^D expresses the solvent isotope-effect on the dissociation constant of an electrically neutral acid, and is expected to lie in the range 2·5—4·5. For acetaldehyde hydrate the corresponding ratio has a value [17] of 4·5. If we consider the general trend of such ratios with acid strength (which holds at least for structurally similar acids [18]), a value between 3 and 3·5 seems reasonable for the hydrate of acetic anhydride. By analogy with other cases,[19] the ratio $(k_3^{H_3O^+})^H/(k^{D_3O^+})^D$ will be close to unity. Accordingly, k_0^H/k_0^D should be mainly governed by the value of K_2^H/K_2^D, and the observed value of 2·9 for the rate ratio agrees with this deduction.

For acetate catalysis the effects on K_{AcOH} and k_3^{AcOH} must also be considered. The former is known fairly accurately [20] ($K^H_{AcOH}/K^D_{AcOD} = 3{\cdot}3$). We can give no soundly based *a priori* estimate for the latter, but it seems reasonably certain that $(k_3^{AcOH})^H/(k_3^{AcOD})^D$ would be greater than $\sqrt{2}$, on the ground that the attachment of the proton (which is being transferred from one oxygen atom to another) would be loosened during the formation of the transition state. The experimental value of $(k_3^{AcOH})^H/(k_3^{AcOD})^D$ is derived as follows. From equations (1) and (2) we deduce that

$$k_{OAc}/k_0 = k_3^{AcOH}/k_3^{H_3O^+} K_{AcOH}, \qquad (3)$$

and hence

$$\frac{(k_3^{AcOH})^H}{(k_3^{AcOD})^D} = \frac{k^D_0}{k^H_0} \cdot \frac{(k_3^{H_3O^+})^H}{(k_3^{D_3O^+})^D} \cdot \frac{k^H_{OAc}}{k^D_{OAc}} \cdot \frac{K^H_{AcOH}}{K^D_{AcOD}}$$

$$= \frac{1}{2{\cdot}9} \times (\sim 1) \times 1{\cdot}7 \times 3{\cdot}3$$

$$\approx 1{\cdot}9,$$

which is compatible with the above consideration.

[16] Bell, *Quart. Rev.*, 1959, **13**, 169.
[17] Pocker, *Proc. Chem. Soc.*, 1960, 17.
[18] Högfeldt and Bigeleisen, *J. Amer. Chem. Soc.*, 1960, **82**, 15.
[19] Long and Watson, *J.*, 1958, 2019.
[20] Korman and La Mer, *J. Amer. Chem. Soc.*, 1936, **58**, 1396; La Mer and Chittum, *ibid.*, p. 1642.

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Equation (3) may also be examined in relation to the Brønsted catalysis law, but the precise conclusion somewhat depends on the convention adopted with regard to the acid strength of the hydrogen ion and the inclusion of the concentration of water in the term for the spontaneous rate. By Bell's usage,[21] equation (3) should in this connection be modified to give

$$55{\cdot}3k_{OAc}/k_0 = k_3^{AcOH}/k_3^{H_3O^+}K_{AcOH}$$

On expressing k_3 as GK^{α} (the statistical factor for the hydrogen ion being taken as unity [21]) and inserting the experimental values, we obtain

$$55{\cdot}3 \times \frac{4{\cdot}6}{2{\cdot}61} = \left(\frac{1{\cdot}75 \times 10^{-5}}{55{\cdot}3}\right)^{\alpha} \cdot \frac{1}{1{\cdot}75 \times 10^{-5}}$$

or

$$(55{\cdot}3)^2 \times \frac{4{\cdot}6}{2{\cdot}61} = \left(\frac{1{\cdot}75 \times 10^{-5}}{55{\cdot}3}\right)^{\alpha-1}$$

whence $\alpha = 0{\cdot}43$. This figure is subject to the uncertainty inherent in the assumptions required, but is probably of some predictive value.

As is well known, the numerical value of the Brønsted exponent decides whether general catalysis is experimentally observable in a given reaction, and the absence of measurable general catalysis does not invalidate a reaction scheme which formally involves general catalysis. The above reaction mechanism may therefore apply to other spontaneous hydrolyses of carbonyl compounds for which large solvent isotope-effects have been observed, even where there is no experimental evidence of catalysis by bases other than water.[22]

Since k_0 is a composite quantity, it follows that the experimental activation energy will be the sum of a number of terms, including the heat of ionisation of the dihydroxy-intermediate. As heats of ionisation are generally temperature-dependent, it is reasonable to suppose that the experimental activation energy should also be markedly temperature-dependent, as was established a number of years ago.[23] The composite nature of the activation energy may also explain its uncommonly small value.[23]

It has previously been remarked [23] that the negative salt effect in this reaction does not seem to be explicable in terms of long-range electrostatic effects. This view is strongly reinforced by our observation that the effect of sodium chloride on the hydrolysis in heavy water is very much less than the effect in ordinary water.

Lest the scope of the above kinetic scheme be misunderstood, we emphasise that our experimental evidence requires solely that the transition state should contain (in a rearranged form) one acetic anhydride, one acetate, and at least one water molecule. The timing of the steps by which these entities come together can be discussed only on the basis of considerations other than those of kinetic orders. The timing implied by the scheme given is preferred to others on the ground of simplicity: it requires no novel mechanistic postulate or steps of molecularity greater than 2 and, as we believe to have shown, it allows us to assign acceptable values to the rate and equilibrium constants involved.

In our discussion we have drawn heavily on analogies with the hydration of acetaldehyde. The analogy also implies that the argument which caused us to admit the possibility of a rate-determining proton transfer to oxygen in the case of acetic anhydride would similarly apply to the mechanisms of the hydration of acetaldehyde. For example, it does not

[21] Bell, " Acid–Base Catalysis," Oxford Univ. Press, 1941, pp. 91, 92.
[22] Butler and Gold, *Chem. and Ind.*, 1960, 1218; cf. Bunton, Fuller, Perry, and Shiner, *Chem. and Ind.*, 1960, 1130.
[23] Gold, *Trans. Faraday Soc.*, 1948, **44**, 506.

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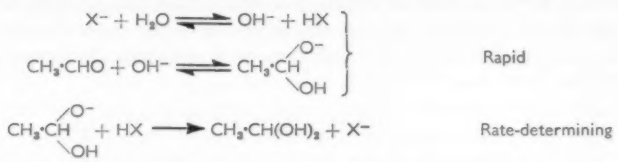
seem possible to dismiss a scheme of the following type for the base (X^-)-catalysed reaction:



solely because the rate constant of the final step is expected to have a large value. We are not here concerned with the issue whether such a scheme would be acceptable on other grounds.

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447. *The Biosynthesis of Phenols. Part III.* Oxidative Coupling leading to Geodoxin and Related Compounds.*

By C. H. HASSALL and J. R. LEWIS.

Geodoxin and related compounds may be synthesised from the corresponding *o*-carboxydiphenyl ethers by intramolecular coupling reactions involving lead dioxide and ammonium ceric sulphate as oxidising agents.

IT has been shown that related strains of *Aspergillus terreus* Thom produce the compounds geodin [1] (IIb), geodoxin [2] (IVb), and asterric acid [3] (IIIa). Further, there is evidence indicating that sulochrin (I), a compound isolated from the culture fluid of the fungus *Oospora sulphurea-ochracea*,[4] is related to the *A. terreus* metabolites: not only is it converted into asterric acid by simple stages [3] that could occur *in vivo* but also there is, in the mycelium of *O. sulphurea-ochracea*, a compound known as Nishikawa's substance A, $C_{17}H_{16}O_8$, that has properties (m. p. 214°; diacetyl derivative, m. p. 147°) identical with those of asterric acid.[5] Although direct comparison has not been possible there seems little doubt that substance A is asterric acid.

Comparison of the structures of sulochrin and the *A. terreus* metabolites suggests that a geodoxin analogue may be synthesised from sulochrin by the annexed sequence. This scheme assumes that the chlorine atoms in geodin and geodoxin are introduced in secondary reactions as has been indicated in the case of griseofulvin.[6]

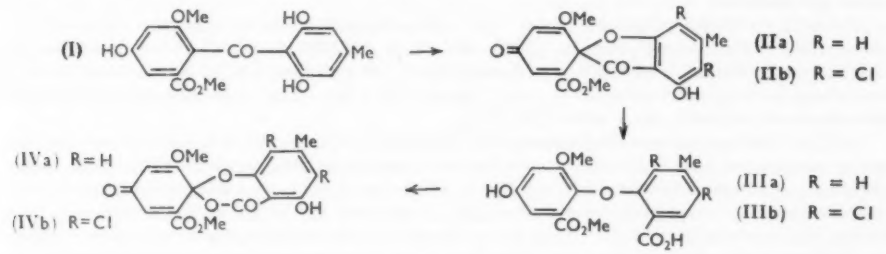
The two steps involved in the conversion of sulochrin into asterric acid have been achieved *in vitro*.[3] It seemed possible that the last stage, the conversion of geodin hydrate (IIIb) into geodoxin was realised *in vivo* by direct oxidative coupling.

To test this route to geodoxin, the simpler acid ether (V) was oxidised under various conditions. Treatment with potassium ferricyanide, which is effective in the oxidative coupling leading to geodin,[7] produced no neutral product in alkaline, acid, or neutral media. However, the use of ammonium ceric sulphate and an active form of lead dioxide [8] yielded the spiran (VI) in 12% and 35% yield respectively. Complementary proof of this

* Part II, *J.*, 1960, 4838.

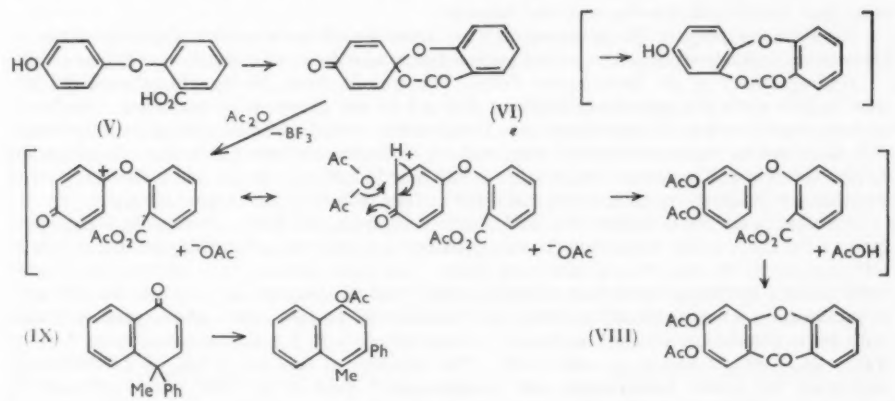
[1] Calam, Clutterbuck, Oxford, and Raistrick, *Biochem. J.*, 1939, **33**, 579.
[2] Hassall and McMorris, *J.*, 1959, 2831.
[3] Curtis, Hassall, Jones, and Williams, *J.*, 1960, 4838.
[4] Nishikawa, *Acta Phytochim., Japan*, 1939, **11**, 167.
[5] Nishikawa, *Bull. Agric. Chem. Soc. Japan*, 1937, **13**, 1; 1942, **18**, 13.
[6] Macmillan, *J.*, 1954, 2585.
[7] Scott, *Proc. Chem. Soc.*, 1958, 195.
[8] Kuhn and Hammer, *Chem. Ber.*, 1950, **83**, 413.

structure came from spectroscopic data and from the fact that hydrogenolysis, with uptake of one mol. of hydrogen, regenerated the acid. A curve obtained by subtracting the ultraviolet absorption curve of salicylic acid from that of the spiran (VI) had $\lambda_{max.}$ 245 mμ (ε 6400). This is consistent with the cross-conjugated dienone system,[2] as is an



infrared band near 1670 cm.$^{-1}$ that has been found also in the spectra of geodin,[9] geodoxin,[2] and picrolichenic acid.[10] The partial synthesis of geodoxin has been achieved in 88% yield by oxidation of the substituted diphenyl ether (IIIb) with lead dioxide. Dechlorogeodoxin (IVa) has been prepared in a similar manner from asterric acid.

There is interest in examining the behaviour of the model spiro-lactone (VI) in the presence of acid as a rearrangement similar to that of the hemiquinone [11] (IX) might lead to a product (VII) analogous to a depsidone. This work is still in progress but one clearly defined case that throws light on the properties of this system deserves mention now. Treatment of the compound (VI) with boron trifluoride in acetic anhydride led to the formation of 2,3-diacetoxyxanthone which was identified by comparison with the xanthone synthesised from 2-carboxy-3′,4′-dimethoxydiphenyl ether. The reaction with boron



trifluoride in acetic anhydride may be interpreted as resulting from attack of the electrophilic " acetylium ion " on the lactone bridge of the spiran. This is followed by redistribution of charge, attachment of the acetate residue to position 3′, and condensation to give xanthone (VIII). There is, then, no indication that under these conditions the 2′-position tends to acquire positive character to favour a shift of the carboxy-group from the 1′- to the 2′-position, leading to the compound (VII).

[9] Barton and Scott, *J.*, 1958, 1767.
[10] Wachtmeister, *Acta Chem. Scand.*, 1958, **12**, 147.
[11] Arnold and Buckley, *J. Amer. Chem. Soc.*, 1949, **71**, 1781.

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Experimental

M. p.s were determined by means of a Kofler block. Ultraviolet spectra were measured for ethanol solutions on a Unicam spectrophotometer. Infrared spectra were measured by Dr. H. E. Hallam and Mr. D. Jones for potassium bromide discs on a Grubb–Parsons double-beam spectrometer.

2-Carboxy-4′-hydroxydiphenyl Ether (V).—2-Carboxy-4′-methoxydiphenyl ether (3 g.; m. p. 146—147°; methyl ester, m. p. 60—62°, b. p. 127°/0·2 mm.), which was prepared by Ungnade and Rubin's method,[12] was demethylated by refluxing glacial acetic acid (30 ml.) containing hydrogen bromide (48% w/w; 10 ml.) for 2 hr. The hydroxy-acid recrystallised from benzene as plates, m. p. 158—159° (2 g.).

1,2,3,4-Tetrahydro-4-oxo-1,3-dioxanaphthalenespirocyclohexa-2′,5′-dien-4′-one (VI).—(a) *By use of ammonium ceric sulphate.* A solution of ammonium ceric sulphate (2·75 g.) in water (50 ml.) was added, dropwise, with vigorous stirring during 1 hr. to a mixture of carbon tetrachloride (50 ml.) and 2-carboxy-4′-hydroxydiphenyl ether (V) (1 g.) in water (250 ml.) containing sodium carbonate (2 g.). After being stirred for a further hour, the solution was acidified and extracted with ether. The extract was washed with water and saturated sodium hydrogen carbonate solution, dried, and evaporated to leave the neutral *compound* (VI) (120 mg., 12%) which, crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 164—166° (Found: C, 68·2; H, 3·8; O, 28·1. $C_{13}H_8O_4$ requires C, 68·4; H, 3·5; O, 28·1%), $\lambda_{max.}$ 240, 298 mμ (ε 8450, 1920). The subtraction curve compound (V) — salicylic acid gave $\lambda_{max.}$ 245 mμ (ε 6400). The infrared spectrum showed maxima at 1745 (lactone) and 1675 cm.$^{-1}$ (conjugated CO).

(b) *By use of lead dioxide.* A mixture of 2-carboxy-4′-hydroxydiphenyl ether (V) (500 mg.), chloroform (10 ml.), ether (5 ml.), and the freshly prepared, active form of lead dioxide (10 g.) was shaken for 16 hr. The solution was filtered; the lead dioxide was washed with ether, and the combined filtrate and washings were extracted with sodium hydrogen carbonate solution to remove unchanged acid. The dried ether extract was evaporated to give a solid, m. p. 164—166° (175 mg., 35%), identical with material obtained in the previous experiment. Acidification of the sodium hydrogen carbonate solution, followed by extraction and working up in the usual way, gave unchanged starting material (20 mg.).

Attempts to prepare the spirolactone (VI) from 2-carboxy-4′-hydroxydiphenyl ether by electrolysis or alkaline potassium ferricyanide or ferric chloride in chloroform, were not successful.

Hydrogenolysis of the Spiro-lactone (VI).—The spiro-lactone (36 mg.) in ethanol (25 ml.) was shaken with 5% palladium–charcoal (0·5 g.) in the presence of hydrogen. Hydrogen (4·1 ml.; 1 mol. = 3·8 ml.) was taken up. Evaporation of the filtered solution gave a solid which was dissolved in ether and washed with sodium hydrogen carbonate solution. Acidification of this solution and extraction with ether led to a solid (23 mg.), m. p. and mixed m. p. with 2-carboxy-4′-hydroxydiphenyl ether, 157—158°. The infrared spectra were identical.

Reaction of the Spiro-lactone (VI) *with Acetic Anhydride and Boron Trifluoride.*—The spiro-lactone (50 mg.), acetic anhydride (10 ml.), and boron trifluoride–ether complex (0·2 ml.) were left together for 30 min., then poured into water. An ether extract of the mixture was washed with sodium hydrogen carbonate solution, dried, and evaporated to give a solid (41 mg.). Crystallisation from methanol–acetone gave needles, m. p. 189—191°, which gave no colour with ferric chloride in aqueous methanol; on admixture with 1,2-diacetoxyxanthone [13] (m. p. 198°; lit., 190°) it had m. p. 165—180°. The identity of this compound as 2,3-diacetoxyxanthone, for which Liebermann and Lindenbaum [14] gave m. p. 186°, was confirmed by hydrolysis with 10% methanolic potassium hydroxide at room temperature, overnight, to 2,3-dihydroxyxanthone which was purified by sublimation at 240°/0·9 mm. to give needles, m. p. 291—194° (Liebermann and Lindenbaum [14] gave m. p. 294°). Treatment of this product (75 mg.) in refluxing acetone (100 ml.) with anhydrous potassium carbonate (5 g.) and dimethyl sulphate (10 ml.) for 12 hr. gave needles, m. p. 163—164° (Found: C, 70·2; H, 4·5; O, 24·7. Calc. for $C_{17}H_{12}O_6$: C, 70·3; H, 4·7; O, 25·0%). The m. p. was undepressed on admixture with authentic 2,3-dimethoxyxanthone, synthesised by the procedure detailed below, and the infrared spectra of the two samples were identical.

[12] Ungnade and Rubin, *J. Org. Chem.*, 1951, **16**, 1311.
[13] Davies, Lamb, and Suschitzky, *J.*, 1958, 1790.
[14] Liebermann and Lindenbaum, *Ber.*, 1904, **37**, 2735.

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2,3-*Dimethoxyxanthone*.—This compound has been prepared by Asahina and Tanase [15] by the treatment of 3,4-dimethoxydiphenyl ether with carbonyl chloride and aluminium chloride, but the details were not available to us. It has also been prepared by Cavill, Robertson, and Whalley [16] by the action of boiling acetyl chloride containing sulphuric acid on an acid, m. p. 174—175°, which was prepared from 3,4-dimethoxydiphenyl ether by the action of zinc cyanide, hydrogen chloride, and aluminium chloride under the usual conditions of the Hoesch synthesis, followed by oxidation of the resulting aldehyde with potassium permanganate. The acid was assumed to be 2-carboxy-3′,4′-dimethoxydiphenyl ether although the method of synthesis left open the alternatives 2′- and 6′-carboxy-3′,4′-dimethoxydiphenyl ether. We have found it convenient to prepare 2-carboxy-3′,4′-dimethoxydiphenyl ether by heating 4-bromoveratrole (22 g.) with sodium methyl salicylate (30 g.; prepared from methyl salicylate and sodium methoxide followed by removal of methanol in a high vacuum) and copper bronze (0·5 g.) at 260° for 1·5 hr. The crude acid fraction (9·5 g.) was obtained by dilution with water, acidification, extraction with ether, washing of the ether layer with sodium hydrogen carbonate solution, and acidification of this alkaline extract. This crude acid with methanol–sulphuric acid gave an oil; on distillation thereof the major fraction (4·5 g.), b. p. 175—178°/1·5 mm., was 2-*methoxycarbonyl*-3′,4′-*dimethoxydiphenyl ether*, m. p. 68—69° (Found: C, 66·6; H, 5·9; O, 27·8. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6; O, 27·8%). Hydrolysis of this methyl ester gave 2-*carboxy*-3′,4′-*dimethoxydiphenyl ether* (4·1 g.) which, crystallised from methanol, had m. p. 149—150° (Found: C, 65·8; H, 5·2; O, 29·0. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·2; O, 29·2%). This compound is evidently different from that, m. p. 174—175°, which was assigned this structure by Cavill *et al.* From the evidence now available their compound must be 6′-carboxy-3′,4′-dimethoxydiphenyl ether.

Cyclisation was accomplished by refluxing 2-carboxy-3′,4′-dimethoxydiphenyl ether (310 mg.) in acetyl chloride (5 ml.) containing concentrated sulphuric acid (5 drops) for 15 min. The mixture was poured on ice and extracted with ether. The ether layer was washed with dilute sodium hydroxide solution, dried, and evaporated to leave a solid (120 mg.) which crystallised from acetone as needles, m. p. 164—165°. Cavill *et al.*[16] record m. p. 164° for 2,3-dimethoxyxanthone.

Partial Synthesis of Geodoxin.—Geodin hydrate [17] (97 mg.) was shaken with ether (20 ml.) and active lead dioxide (1 g.) for 2 hr. The mixture was filtered and the dioxide was washed with fresh ether. Evaporation of the combined filtrate and washings gave geodoxin (86 mg., 88%) which, crystallised from chloroform–pentane, had m. p. and mixed m. p. 211—212°. The infrared spectrum was authentic.

Dechlorogeodoxin (IVa).—A mixture of asterric acid (IIIc) (100 mg.), ether (5 ml.), and lead dioxide (2·5 g.) was shaken for 3 hr. Working up as in the previous experiment gave *dechlorogeodoxin* (70 mg., 71%), which crystallised from benzene–pentane as a pale yellow solid, m. p. 170—173° (Found: C, 58·8; H, 4·2; O, 36·5. $C_{17}H_{14}O_8$ requires C, 59·0; H, 4·1; O, 37·0%), $\lambda_{max.}$ 265, 318 mμ (ε 12,980, 7470). The subtraction curve dechlorogeodoxin − *p*-orsellinic acid gave $\lambda_{max.}$ 270, 328 mμ (ε 11,500, 5800). The infrared spectrum showed bands at 1730 (lactone and CO_2Me) and 1670 cm.$^{-1}$ (conjugated CO).

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Department of Chemistry,
University College of Swansea. [*Received, November 25th*, 1960.]

[15] Asahina and Tanase, *Proc. Imp. Acad. Tokyo*, 1940, **16**, 297; *Chem. Abs.*, 1940, **34**, 7096.
[16] Cavill, Robertson, and Whalley, *J.*, 1949, 1567.
[17] Calam, Clutterbuck, Oxford, and Raistrick, *Biochem. J.*, 1947, **41**, 458.

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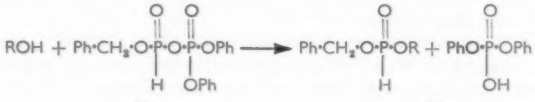
448. *Nucleotides. Part XLVI.*[1] *A New Method for the Preparation of Nucleoside Phosphites.*

By J. A. Schofield and Sir Alexander Todd.

Nucleoside phosphites can be prepared in good yield by reaction of nucleosides with phosphorous acid and stoicheiometric proportions of di-*p*-tolylcarbodi-imide in dry pyridine; no esterification occurs under these conditions when monobenzyl phosphite is used in place of phosphorous acid. The mechanism of the reaction is discussed. Preparation of deoxyadenosine-5′ phosphite by this method followed by permanganate oxidation gives deoxyadenosine-5′ phosphate in an overall yield of 40%.

Most of the recorded monoalkyl esters of phosphorous acid have been prepared by treating the appropriate alcohol with phosphorus trichloride and hydrolysing the resulting phosphorochloridite. Although many monoalkyl phosphites have been prepared in this way,[2] the method is not very suitable for preparing the phosphites of relatively sensitive substances such as nucleosides. Nucleoside benzyl phosphites (II; R = nucleoside residue) have, however, been prepared by reaction of a suitably protected nucleoside with the mixed anhydride (I) obtained by treating monobenzyl phosphite with diphenyl phosphorochloridate; the simple nucleoside phosphite could then be obtained from the product by anionic debenzylation and removal of protecting groups.[3] The yields obtained by this method are usually indifferent, particularly when stoicheiometric amounts of reagents are employed. Recently Tanaka [4] has described the preparation of both riboflavin-5′ phosphite and pyridoxin phosphite using as reagent either diphenyl phosphorochloridite or the cyclic phosphorochloridite prepared from salicylic acid and phosphorus trichloride; protecting groups were in each case removed by hydrolysis and the products were then converted into the corresponding phosphates by oxidation with potassium permanganate. In view of the potential interest of the nucleoside phosphites in various studies relating to nucleic acid chemistry, there is clearly a need for better preparative procedures.



(I) (II)

We have now shown that treatment of an alcohol with phosphorous acid and di-*p*-tolylcarbodi-imide in dry pyridine solution yields the corresponding monoalkyl phosphite directly. The reaction appears to be generally applicable and it gives high yields even when stoicheiometric amounts of reactants are employed. By this method the 2′,3′-*O*-isopropylidene derivatives of adenosine and uridine were converted into the corresponding 5′-phosphites in yields of approximately 78% and 74% respectively. When 5′-*O*-trityl-thymidine was treated in the same way and the product heated for a short time with 80% acetic acid to remove the trityl group, thymidine-3′ phosphite was isolated (as its ammonium salt) in *ca.* 40% yield. The relatively low yield in this instance is undoubtedly due to hydrolytic removal of the phosphite group during the acid treatment; model experiments have shown that the phosphite is completely hydrolysed in 1 hr. by hot 80% acetic acid.

Treatment of thymidine itself with phosphorous acid and di-*p*-tolylcarbodi-imide gave a mixture of the 3′-phosphite (43%) and 5′-phosphite (24%), while deoxyadenosine gave a

[1] Part XLV, Baluja, Chase, Kenner, and Todd, *J.*, 1960, 4678.
[2] Kosolapoff, "Organophosphorus Compounds," Wiley, New York, 1950, p. 201.
[3] Hall, Todd, and Webb, *J.*, 1957, 3291.
[4] Tanaka, *J. Pharm. Soc. Japan*, 1959, **79**, 437, 721, 1301.

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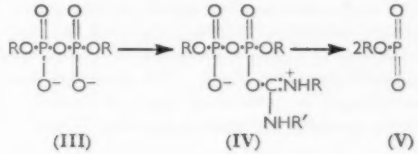
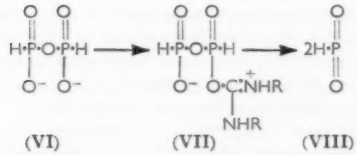
larger proportion of the 5′-phosphite (42%) than of the 3′-phosphite (29%). The isomeric deoxyadenosine phosphites could be separated, on a preparative scale, by chromatography on a column of ECTEOLA cellulose. Attempts to oxidise the thymidine phosphites to the corresponding phosphates with potassium permanganate gave only traces of the desired products; paper chromatography showed that destruction of the heterocyclic nucleus had occurred and the main product was a phosphorus-containing material showing no ultraviolet absorption. Similar destruction of the nucleus occurred when thymidine-5′ phosphate and deoxycytidine-5′ phosphate were treated with permanganate under the same conditions. Jones and his co-workers [5] have shown that the ease of oxidation of the bases occurring in deoxyribonucleic acid is in the order cytosine and thymine > guanine ≫ adenine. In accordance with this 2′,3′-*O*-isopropylideneadenosine-5′ phosphite and the isomeric deoxyadenosine phosphites were oxidised by permanganate to give the corresponding phosphates in good yield.

The fact that nucleosides are converted into monoesters of phosphorous acid so smoothly by the method described prompted us to examine again their conversion into nucleoside benzyl phosphites. Reaction of monobenzyl phosphite with either diphenyl phosphorochloridate or toluene-*p*-sulphonyl chloride in presence of a stoicheiometric amount of 2′,3′-*O*-isopropylideneadenosine and 3 mols. of base gave 2′,3′-*O*-isopropylideneadenosine-5′ benzyl phosphite in only *ca.* 30% yield. When the same nucleoside was treated in stoicheiometric proportion with monobenzyl phosphite and di-*p*-tolylcarbodi-imide in pyridine solution only traces of phosphite were formed.

This striking difference between the preparation of mono- and di-esters of phosphorous acid recalls the marked difference between the reactivity towards alcohols of the mono- and di-esters of phosphoric acid in presence of carbodi-imides. One of us [6] has sought to explain the latter difference by postulating that reaction of a monoester of phosphoric acid with a carbodi-imide yields first the P^1P^2-diester of pyrophosphoric acid (III), which then reacts with a further molecule of carbodi-imide to yield an isouronium pyrophosphate represented in its protonated form by (IV). This product (IV) then breaks down, yielding



(III) (IV) (V)



(VI) (VII) (VIII)

2 mols. of the hypothetical monomeric metaphosphate (V) which is the true phosphorylating agent and reacts with an alcohol to yield a diester of phosphoric acid. This explains why monoesters of phosphoric acid are readily converted into diesters by this means,[7] whereas diesters of phosphoric acid, which cannot generate metaphosphate in this way, react with alcohols in presence of carbodi-imides only with difficulty unless the alcohol is

[5] Bayley and Jones, *Trans. Faraday Soc.*, 1959, **55**, 492; Benn, Chatamra, and Jones, *J.*, 1960, 1014.

[6] Todd, *Proc. Acad. Nat. Sci. U.S.A.*, 1959, **45**, 1389.

[7] Gilham and Khorana, *J. Amer. Chem. Soc.*, 1958, **80**, 6212; 1959, **81**, 4647; Tener, Khorana, Markham, and Pol, *ibid.*, 1958, **80**, 6223.

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present in overwhelming excess (*e.g.*, as solvent for the reaction). By analogy with this scheme, the reaction of phosphorous acid with a carbodi-imide should yield pyrophosphorous acid (VI) which would presumably react further to give the protonated intermediate (VII). Disruption of the latter would give 2 mols. of (VIII) which is the phosphite (or phosphonate) analogue of the metaphosphate (V) and should react readily with alcohols to yield monoesters of phosphorous acid. Monoesters of phosphorous acid cannot yield a compound of type (VIII) and hence should be, as observed, very indifferent reagents towards alcohols in presence of carbodi-imides. It is interesting that, when thymidine was treated with phosphoric acid and di-*p*-tolylcarbodi-imide in pyridine under the conditions used for phosphorous acid, no phosphorylated material could be detected by paper chromatography. On the mechanism suggested above, metaphosphoric acid should be produced in this reaction; however, in pyridine solution it would almost certainly be in the form of its anion which would not be a favourable phosphorylating agent for alcohols.

Experimental

Materials for analysis were dried at 80°/10^{-2} mm. for 8 hr.

Paper Chromatography.—Unless otherwise stated, data given refer to ascending chromatograms on Whatman No. 1 paper in the solvent system propan-2-ol–ammonia (*d* 0·88)–water (7 : 1 : 2). In the text, solvent system A refers to butan-1-ol–acetic acid–water (5 : 2 : 3) and system B to propan-2-ol–ammonia (*d* 0·88)–acetic acid–water (4 : 1 : 2 : 2).

2′,3′-O-Isopropylideneadenosine-5′ Phosphite.—A mixture of crystalline phosphorous acid (28 mg., 0·33 mmole) and 2′,3′-*O*-isopropylideneadenosine (102·3 mg., 0·33 mmole) was thoroughly dried by thrice dissolving it in dry pyridine and evaporating the solution at 10^{-2} mm. The dried mixture was then dissolved in dry pyridine (8 ml.), di-*p*-tolylcarbodi-imide (80 mg., 0·37 mmole) was added, and the mixture left for 72 hr. at room temperature, moisture being excluded. Paper chromatography showed the product to contain a little 2′,3′-*O*-isopropylideneadenosine (R_F 0·93) and phosphorous acid (R_F 0·13) with a new substance (R_F 0·72) as the main constituent. The mixture was poured into water (20 ml.) and filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in a little water, and the solution streaked on four sheets (11 cm. width) of Whatman No. 3 paper. The chromatographs were developed in the usual way and the main band cut out, eluted with dilute ammonia, and lyophilised to give *ammonium 2′,3′-O-isopropylideneadenosine-5′ phosphite* (101·5 mg., 78%) as a slightly yellowish glass. This material was dissolved in a minimum of ethanol, the solution centrifuged to remove a trace of insoluble material, and the product reprecipitated with ether as a white amorphous powder (Found: P, 8·1. $C_{13}H_{17}N_5O_6P,NH_4$ requires P, 8·0%).

The above product (5·8 mg.) was dissolved in 0·015% aqueous sodium hydrogen carbonate (1 ml.), and 0·155% aqueous potassium permanganate (1 ml.) was added dropwise during 1 hr. The mixture was set aside for 6 hr., then evaporated to dryness. The residue was taken up in a little water, Amberlite IR-120 (pyridinium form) added, and the whole filtered. Paper-chromatographic examination of the filtrate showed that it contained a product identical in R_F (0·29) with 2′,3′-*O*-isopropylideneadenosine-5′ phosphate.

2′,3′-O-Isopropylideneuridine-5′ Phosphite.—A mixture of 2′,3′-*O*-isopropylideneuridine (95 mg., 1 mol.) and phosphorous acid (28 mg., 1 mol.), dried as above by thrice evaporating it with pyridine, was dissolved in pyridine (5 ml.), and di-*p*-tolylcarbodi-imide (80 mg., 1·1 mol.) was added. After 24 hr., paper chromatography showed the presence of small amounts of unchanged starting material (R_F 0·58) and phosphorous acid (R_F 0·24), with a new substance (R_F 0·87) as the major component. Worked up as in the previous experiment *ammonium 2′,3′-O-isopropylideneuridine-5′ phosphite* (91·4 mg., 74%) was obtained as a white amorphous powder (Found: P, 8·2. $C_{12}H_{16}N_2O_8P,NH_4$ requires P, 8·5%).

Thymidine-3′ Phosphite.—A mixture of 5′-*O*-tritylthymidine (121 mg., 1 mol.) and phosphorous acid (20·5 mg., 1 mol.) was dried in the usual way, then dissolved in dry pyridine (5 ml.). Di-*p*-tolylcarbodi-imide (70 mg., 1·2 mol.) was added and the solution set aside for 20 hr. at room temperature, moisture being excluded. The mixture was then evaporated and the residue heated in aqueous 80% acetic acid (5 ml.) at 70° for 15 min. to remove the trityl

group. This solution was next evaporated under reduced pressure, and a solution of the residue in a little pyridine (5 ml.) was poured into water (20 ml.), filtered from the precipitated di-*p*-tolylurea and triphenylmethanol, and concentrated to small bulk. Paper chromatography of a sample showed three phosphorus-containing compounds: (*a*) R_F 0·62 (main product), (*b*) R_F 0·46 (trace), and (*c*) phosphorous acid, R_F 0·27. The remainder of the solution was streaked on two sheets (13 cm. width) of Whatman No. 3 paper and after chromatographic development the main band was cut out and eluted with aqueous ammonia. The eluate was lyophilised and the product purified by dissolution in ethanol and reprecipitation with ether. *Ammonium thymidine-3′ phosphite* (33·8 mg., 40%) was obtained as a white amorphous powder (Found: P, 8·8. $C_{10}H_{14}N_2O_7PNH_4,H_2O$ requires P, 9·1%).

Thymidine-3′ and Thymidine-5′ Phosphite from Thymidine.—A dried mixture of thymidine (81 mg., 1 mol.) and phosphorous acid (35 mg., 1·3 mol.) was dissolved in pyridine (3 ml.) and, after addition of di-*p*-tolylcarbodi-imide (100 mg., 1·4 mol.), was left at room temperature for 3 days, moisture being excluded. In addition to some unchanged starting materials the product contained two major phosphorus-containing and ultraviolet-absorbing spots (R_F 0·71 and 0·53). The mixture was worked up as before by preparative chromatography on Whatman No. 3 paper. Elution of the faster-moving band (R_F 0·71) and isolation of the white amorphous salt gave ammonium thymidine-3′ phosphite (49 mg., 43%), indistinguishable by paper chromatography from the material prepared above from 5′-*O*-tritylthymidine (Found: P, 9·5. Calc. for $C_{10}H_{14}N_2O_7P,NH_4,H_2O$: P, 9·1%).

Worked up in the same fashion, the slower-moving band (R_F 0·53) gave *ammonium thymidine-5′ phosphite* (27 mg., 24%) (Found: P, 9·45%).

Deoxyadenosine Phosphites.—Deoxyadenosine (85 mg., 1 mol.) was treated with phosphorous acid (38 mg., 1·4 mol.) and di-*p*-tolylcarbodi-imide (100 mg., 1·4 mol.) in pyridine (3 ml.), exactly as was thymidine in the above experiment, and the products were worked up in the same way, yielding as major product, *ammonium deoxyadenosine-5′ phosphite* (52 mg., 42%) (Found: P, 8·95. $C_{10}H_{13}N_5O_5P,NH_4,H_2O$ requires P, 8·9%). This product had R_F 0·59 and on oxidation with permanganate gave deoxyadenosine-5′ phosphate identified by comparison with an authentic specimen. The lesser product (R_F 0·46) from the reaction was isolated as *ammonium deoxyadenosine-3′ phosphite* (36 mg., 29%), oxidised by permanganate to deoxyadenosine-3′ phosphate (Found: P, 8·6%).

In a further experiment the reaction mixture (from deoxyadenosine, 0·425 g.), after removal of di-*p*-tolylurea by filtration, was stirred with charcoal (15 g.) for 1 hr. and then filtered. The charcoal was washed with water and extracted with boiling ethanolic ammonia (2 × 100 ml.). The combined extracts were evaporated to dryness and the residue was dissolved in methanol (25 ml.). Addition of ether precipitated a white solid (362·5 mg.) which was separated by centrifugation.

A portion (200 mg.) of this material was dissolved in water (10 ml.) and was added to a column (27 × 2 cm.) of ECTEOLA cellulose (chloride form). Elution with 0·025M-lithium chloride gave fraction A, which was evaporated to dryness. The residue was dissolved in the minimum amount of 95% ethanol. Addition of excess of acetone precipitated *lithium deoxyadenosine-5′ phosphite* (158·9 mg.) as a white powder (Found, in material dried for 15 hr.: P, 9·9. $C_{10}H_{13}LiN_5O_5P$ requires P, 9·7%).

Further elution of the column with 0·05M-lithium chloride gave fraction B, which was worked up as above to give crude lithium deoxyadenosine-3′ phosphite (55·2 mg.) as a white powder.

Deoxyadenosine-5′ Phosphate.—The lithium salt of deoxyadenosine-5′ phosphite (64 mg.), prepared as described above, was dissolved in water (5 ml.) containing sodium hydrogen carbonate (20 mg.). The solution was cooled in ice, and 0·155% aqueous potassium permanganate (13 ml.) was added during 45 min. with stirring. The mixture was filtered, and inorganic cations were removed with Amberlite IR-120 (pyridinium form). The resulting solution was evaporated to dryness, and the residue evaporated once with dilute ammonia, dissolved in water (10 ml.), and put on a column (20 × 2 cm.) of ECTEOLA cellulose (chloride form). Elution was carried out by a linear gradient technique with water (500 ml.) in the mixing vessel and an equal volume of 0·1M-lithium chloride. The main fraction was evaporated and the residue dissolved in a minimum of water. Addition of ethanol (5 ml.) followed by acetone (30 ml.) precipitated *dilithium deoxyadenosine-5′ phosphate* (48·6 mg.) as a white powder (Found: P, 8·6. $C_{10}H_{12}Li_2N_5O_6P$ requires P, 9·0%). The nucleotide obtained in this way

was identical in chromatographic behaviour with authentic deoxyadenosine-5′ phosphate, running as a single spot (R_F 0·16) in propan-2-ol–ammonia (*d* 0·88)–water, R_F 0·23 in system A and R_F 0·63 in system B. Treatment with rattlesnake venom [8] (*C. atrox*) for 3 hr. at 37 converted the product smoothly into deoxyadenosine (R_F 0·7).

Deoxyadenosine-3′ Phosphate.—The crude lithium salt of deoxyadenosine-3′ phosphite, prepared as above, was oxidised and the product worked up as was the 5′-compound. Paper chromatography showed the presence of two compounds (R_F 0·11 and 0·02). The faster-running compound was identical with authentic deoxyadenosine-3′ phosphate; treatment with rattlesnake venom had virtually no effect, only a trace of deoxyadenosine being produced. The slower-moving compound is probably deoxyadenosine-3′,5′ diphosphate.

This work was carried out during the tenure (by J. A. S.) of an I.C.I. Fellowship.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 21st*, 1960.]

[8] Michelson and Todd, *J.*, 1953, 951.

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449. *Tropylium Complex Halide Salts of Boron, Aluminium, Iron, Titanium, and Tin.*

By D. BRYCE-SMITH and N. A. PERKINS.

Interaction of cycloheptatriene and t-butyl chloride in the presence of BCl_3, Al_2Cl_6, Fe_2Cl_6, and $SnCl_4$, respectively, gives the tropylium salts $C_7H_7^+BCl_4^-$, $C_7H_7^+AlCl_4^-$, $C_7H_7^+FeCl_4^-$, and $(C_7H_7)_2^{2+}SnCl_6^{2-}$. The use of titanium tetrachloride gives a product believed to be $C_7H_7^+TiCl_5^-$. Silicon tetrachloride shows very slight catalytic activity. Reaction between cycloheptatriene and t-butyl chloride does not occur in the absence of catalysts. Salts of the above type are also formed by metathesis, *e.g.*, between $C_7H_7^+Br^-$ and $(NH_4)_2^{2+}SnCl_6^{2-}$, or by direct addition, *e.g.*, of $C_7H_7^+Cl^-$ to $SnCl_4$.

ABSTRACTION of hydride from the methylene group in cycloheptatriene, C_7H_8, gives the tropylium ion, $C_7H_7^+$. Dauben, Gadecki, Harmon, and Pearson [1] accomplished this in the reaction of cycloheptatriene with triphenylmethyl perchlorate and fluoroborate in acetonitrile to give the corresponding tropylium salts. Triphenylmethyl halides were reported not to act as satisfactory hydride-acceptors in acetonitrile, but gave high yields of tropylium halides in liquid sulphur dioxide. Halide-hydride exchange, recently reviewed,[2] is known to be often catalysed by acids. For example, Bartlett, Condon, and Schneider [3] showed that aluminium bromide catalysed such exchange between t-butyl chloride and isopentane or isobutane. Volpin and his co-workers [4] have reported extensive studies on the interaction between cycloheptatriene and various acids and inorganic halides to give tropylium salts, some in high yields; but few preparative details and analyses of products have so far been recorded.

The present paper deals with halide-hydride exchange between cycloheptatriene and t-butyl chloride in the presence of various inorganic halides. No uncatalysed reaction between cycloheptatriene and t-butyl chloride could be detected; but in the presence of those halides which can function as Lewis acids, tropylium salts were readily formed. Thus stannic chloride (cf. Bryce-Smith and Perkins [5]), stannic bromide, aluminium chloride, boron trichloride, and ferric chloride, respectively, gave the following salts: $(C_7H_7)_2^{2+}SnCl_6^{2-}$, $(C_7H_7)_2^{2+}SnBr_6^{2-}$ (from t-butyl bromide), $C_7H_7^+AlCl_4^-$, $C_7H_7^+BCl_4^-$, and $C_7H_7^+FeCl_4^-$. The stannichloride was a colourless solid, essentially insoluble in water,

[1] Dauben, Gadecki, Harmon, and Pearson, *J. Amer. Chem. Soc.*, 1957, **79**, 4557.
[2] Deno, Peterson, and Saines, *Chem. Rev.*, 1960, **60**, 7.
[3] Bartlett, Condon, and Schneider, *J. Amer. Chem. Soc.*, 1944, **66**, 1531.
[4] (a) Kursanov and Volpin, *Doklady Akad. Nauk S.S.S.R.*, 1957, **113**, 339; (b) Kursanov, Volpin, and Parnes, *Khim. Nauk i Prom.*, 1958, **3**, 159; (c) Volpin, *Uspekhi Khim.*, 1960, **29**, 298.
[5] Bryce-Smith and Perkins, *Chem. and Ind.*, 1959, 1022.

ethanol, ether, acetone, and hydrocarbons. It was not hygroscopic and showed no tendency to react with oxygen-containing media. The stannibromide was yellow, but otherwise similar to the stannichloride (cf. tropylium bromide and chloride [6]). The colourless deliquescent tetrachloroaluminate resembled the corresponding alkali-metal salts [7] in its failure to form complexes of higher co-ordination number under the conditions employed. Its freshly-prepared aqueous solution was pink, but the colour slowly faded; the pink solution in ethanol did not fade. It was insoluble in ether and hydrocarbons, and did not form an etherate. The colourless deliquescent tetrachloroborate was soluble in ethanol, but insoluble in ether and hydrocarbons, and did not form an etherate. The yellow tetrachloroferrate was not deliquescent, but was freely soluble in water and acetone, sparingly soluble in boiling ethanol, and insoluble in ether and hydrocarbons. All of these salts were soluble in dilute hydrochloric acid, and the solutions showed the ultraviolet spectrum of the tropylium ion.[6]

Titanium tetrachloride, t-butyl chloride, and cycloheptatriene readily gave a yellow solid, which turned colourless in air, gave colourless non-reducing solutions in water or ethanol, and when treated with ether gave a colourless ether-insoluble product, probably an etherate. The yellow compound was insoluble in hydrocarbons. Its aqueous solution was shown to contain tropylium ions by the ultraviolet spectrum,[6] the reaction with sodium tetraphenylboron to give tropylium tetraphenylboron,[8] and the formation of di(cycloheptatrienyl) ether by the action of sodium hydrogen carbonate. Elemental analysis proved extremely difficult, but structures such as the expected $(C_7H_7)_2^{2+}TiCl_6^{2-}$, or $C_7H_7TiCl_3$ were ruled out. The compound is probably $C_7H_7^+TiCl_5^-$. The pentachlorotitanate ion is novel, and is isoelectronic with the as yet unknown vanadium pentachloride. Vanadium pentafluoride is well known, as are the pentachlorides of niobium and tantalum. A search of the literature has revealed only one previous example of quinqueco-ordinate titanium, *viz.*, the $TiCl_5^{2-}$ ion, which Erlich *et al.*[9] have shown to exist in the system $KCl–TiCl_3$.

A mixture of silicon tetrachloride, t-butyl chloride, and cycloheptatriene in hexane very slowly formed tropylium ions, although no definite complex was isolated. Tropylium ions were not found when phosphorus trichloride was used in place of silicon tetrachloride. It seems possible that catalysis of the formation of tropylium ion from cycloheptatriene in the presence of t-butyl chloride may provide a very sensitive test for a Lewis acid.

All the above complex halides were also prepared by direct addition of a tropylium halide to the appropriate inorganic halide, *e.g.*, $2C_7H_7^+Cl^- + SnCl_4 \longrightarrow (C_7H_7)_2^{2+}SnCl_6^{2-}$. In addition, tropylium stannichloride was prepared by double decomposition of tropylium bromide and ammonium stannichloride in alcohol.

Since the activity of the foregoing inorganic halides in promoting the formation of tropylium salts from cycloheptatriene and t-butyl chloride appears related qualitatively to their acceptor properties, *i.e.*, to their activity as Lewis acids, it seems probable that the overall reaction may be an acid-catalysed halide-hydride exchange. In the case (say) of boron trichloride, the following mechanism appears plausible (cf. ref. 4):

$$C_7H_8 + BCl_3 \rightleftharpoons C_7H_7^+BHCl_3^- \quad \ldots\ldots\ldots\ldots \quad (1)$$

$$C_7H_7^+BHCl_3^- + Bu^tCl \longrightarrow C_7H_7^+BCl_4^- + Bu^tH \quad \ldots\ldots\ldots \quad (2)$$

The question whether tropylium halides were formed as intermediates cannot be definitely decided on the evidence available. Were they so formed, which we think improbable, it is established that reaction with free inorganic halide would give the complex salts actually isolated. In the absence of t-butyl chloride, stannic chloride and cycloheptatriene gave a very low yield of tropylium stannichloride. This suggests that stannic

[6] Doering and Knox, *J. Amer. Chem. Soc.*, 1954, **76**, 3203.
[7] Malquori, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1927, **5**, 510; 1928, **7**, 745.
[8] Volpin, Zhdanov, and Kursanov, *Doklady Akad. Nauk S.S.S.R.*, 1957, **112**, 264.
[9] Erlich, Kaupa, and Blankerstein, *Z. anorg. Chem.*, 1959, **299**, 213.

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chloride itself, or some chlorine-containing by-product, can act as chloride donor as in equation (2) above. Allyl chloride was much less effective than t-butyl chloride as a chloride-donor.

Hydrolysis of Tropylium Stannichloride.—Cycloheptatrienol apparently unknown pure, is stated to form di(cycloheptatrienyl) ether at high pH.[6] In accordance with this, tropylium stannichloride was readily decomposed by cold aqueous sodium hydroxide to give moderate yields of the ether. Higher yields were obtained by the use of cold aqueous sodium hydrogen carbonate, but the reason for this is not clear. Bickel [10] found, and we have confirmed, that the ether is stable to aqueous sodium hydroxide, and that this reagent serves to remove the cycloheptatrienone which is liable to be formed when acidic conditions exist during the hydrolysis of tropylium salts.[11,12] We found that the ether formed by all our procedures of alkaline hydrolysis usually contained a few per cent. of the ketone, as recognised by the absorption peak at 6·3 μ in the infrared spectrum. This was eventually traced to the use of acid-washed glassware in the final distillation stage. The use of alkali-washed glassware gave the ether completely free from cycloheptatrienone.

[*Added in proof.*] We have now found that Kursanov and Volpin's supposed preparation of tropylium chloride [4a] in fact gives a complex tropylium salt which contains phosphorus. This is similar to tropylium chloride in several physical and chemical properties, and is under investigation. A few of the results in this paper are affected, but not to an important extent since the compositions of the products have been determined without reference to the starting materials.

Experimental

Materials.—t-Butyl chloride was freshly fractionated before use and had b. p. 50—51°. t-Butyl bromide was prepared and purified as described by Bryce-Smith and Howlett.[13] Silicon tetrachloride, b. p. 57—58°; stannic chloride, b. p. 112—114°; and titanium tetrachloride, b. p. 134—137°, were refractionated before use. The other inorganic halides were commercial materials of good quality.

Cycloheptatriene (International Shell Petroleum Company) was about 93% pure after redistillation. Yields have not been corrected for this. Traces of a yellow compound invariably codistilled, but could be removed by treatment with sodium methoxide or ammonia. The colour arose from a small peak at *ca.* 357 mμ which tailed into the visible. This, coupled with the sensitivity to bases, suggests that the impurity was a methylfulvene: cf. the reported [14] $\lambda_{max.}$ = 355 mμ. All solvents were dried before use, and anhydrous conditions were maintained during experiments as far as possible. All compounds formulated as tropylium salts showed the ultraviolet spectrum of the tropylium ion in 2N-hydrochloric acid.[6]

Preparation of Tropylium Stannichloride.—(a) *From cycloheptatriene, t-butyl chloride, and stannic chloride.* Experimental details and analytical results have been given.[5] The ultraviolet absorption data recorded therein for the 0·005% solution in 2N-hydrochloric acid were incorrectly calculated, and should be replaced by the following values: $\lambda_{min.}$ 258—259 mμ (log $\varepsilon_{min.}$ 3·34); $\lambda_{max.}$ 276—277 mμ (log $\varepsilon_{max.}$ 3·61). The m. p. was 252° (decomp.), and the yield 33% of theoretical.

(b) *From cycloheptatriene, allyl chloride, and stannic chloride.* The use of an equivalent proportion of allyl chloride in place of t-butyl chloride in (a) gave a 5% yield of tropylium stannichloride, m. p. 248° (decomp.) (Found: Sn, 23·2; Cl, 40·8. Calc. for $C_{14}H_{14}Cl_6Sn$: Sn, 23·1; Cl, 41·45%).

(c) *From cycloheptatriene and stannic chloride.* Stannic chloride (19·5 g., 0·075 mole) was added with stirring during 20 min. to a refluxing mixture of cycloheptatriene (13·8 g., 0·15 mole) and hexane (75 ml.). The resulting dark yellow solution was heated under reflux for a further 4½ hr. Filtration, followed by washing of the solid with dry ether (Soxhlet), gave tropylium stannichloride (0·97 g., 2·5% of theoretical), m. p. 251° (decomp.) [Found: C, 33·6; H, 2·95;

[10] Bickel, private communication.
[11] Ter Borg, van Helden, Bickel, Renold, and Dreiding, *Helv. Chim. Acta*, 1960, **43**, 457.
[12] Ikemi, Nozoe, and Sugiyama, *Chem. and Ind.*, 1960, 932.
[13] Bryce-Smith and Howlett, *J.*, 1951, 1141.
[14] Angus, Blair, and Bryce-Smith, *J.*, 1960, 2003.

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Cl, 40·6; Sn, 22·9. Calc. for $C_{14}H_{14}Cl_6Sn$: C, 32·7; H, 2·75; Cl, 41·45; Sn, 23·1%. This analysis rules out any possibility that the product was $(C_7H_7)_2^{2+}SnCl_4H_2^{2-}$, which would require C, 37·8; H, 3·6; Cl, 31·9; Sn, 26·7%; but the presence of traces of such a salt would largely account for the mediocre analytical data].

(d) *From tropylium bromide and ammonium stannichloride.* A solution of tropylium bromide [15] (3·0 g.) in ethanol (35 ml.) was added dropwise to a hot solution of ammonium stannichloride (3·22 g.) in ethanol (300 ml.). The off-white precipitate was purified as in method (c) to give tropylium stannichloride (2·18 g., 48·5%), m. p. 253° (decomp.) (Found: C, 32·4; H, 2·7; Cl, 40·9; Sn, 23·1%).

(e) *From tropylium chloride and stannic chloride.* A solution of tropylium chloride [4a] (1·52 g., 0·012 mole) in ethanol (45 ml.) was added with stirring at room temperature to a solution of stannic chloride (1·56 g., 0·006 mole) in ethanol (45 ml.). The white precipitate which immediately formed was filtered off and washed successively with ethanol and ether (yield 2·27 g., 74%), m. p. 254° (decomp.) (Found: C, 32·9; H, 2·8; Cl, 40·6; Sn, 23·0%).

Preparation of Tropylium Stannibromide.—(a) *From cycloheptatriene, t-butyl bromide, and stannic bromide.* The procedure closely followed (a) above for the stannichloride, except that equivalent proportions of bromides were used in place of chlorides. The *product*, m. p. 249° (decomp.), a yellow solid, insoluble in water and common organic solvents, was obtained in 12% yield (Found: C, 21·4; H, 1·7; Br, 60·7; Sn, 15·2. Calc. for $C_{14}H_{14}Br_6Sn$: C, 21·6; H, 1·8; Br, 61·4; Sn, 15·2%).

(b) *From tropylium bromide and stannic bromide.* A solution of stannic bromide (1·1 g., 0·0025 mole) in ethanol (30 ml.) was added to a solution of tropylium bromide (0·86 g., 0·005 mole) in ethanol (30 ml.). The yellow precipitate was filtered off and washed successively with ethanol and ether. It had m. p. 253° (decomp.) (yield 1·68 g., 86%) (Found: C, 21·4; H, 2·5; Br, 61·8; Sn, 15·1%.)

The compounds $(C_7H_7)_2^{2+}SnBr_2Cl_4^{2-}$ and $(C_7H_7)_2^{2+}SnBr_4Cl_2^{2-}$ were similarly prepared by direct addition of the corresponding halides in ethanol; they had m. p.s 242° and 246°, respectively. The compositions were confirmed by elemental analyses. The physical properties were closely similar to those of the other stannihalides.

Preparation of Tropylium Tetrachloroborate.—(a) *From cycloheptatriene, t-butyl chloride, and boron trichloride.* A mixture of cycloheptatriene (18·4 g.), t-butyl chloride (18·6 g.), boron trichloride (23·5 g.), and hexane (50 ml.) was stirred at room temperature for 6 hr. (cold-finger condenser at −70°). The white precipitate was extracted with ether (Soxhlet) and dried at room temperature *in vacuo*. The *product* (2·8 g., 6%), m. p. 180—190° (decomp.: rather indefinite), was deliquescent, and soluble in water, acetone, and ethanol, but insoluble in ether and hydrocarbons (Found: C, 34·8; H, 3·3; Cl, 57·9. $C_7H_7Cl_4B$ requires C, 34·5; H, 2·9; Cl, 58·2%).

(b) *From tropylium chloride and boron trichloride.* A mixture of tropylium chloride (0·75 g.) and boron trichloride (0·8 g.) was kept at room temperature for 4 days in a sealed tube under nitrogen. Ether extraction (Soxhlet) of the product gave tropylium tetrachloroborate (1·19 g., 82%) as a colourless solid, m. p. *ca.* 180° (Found: C, 34·8; H, 3·3%).

Preparation of Tropylium Tetrachloroaluminate.—(a) *From cycloheptatriene, t-butyl chloride, and aluminium chloride.* A mixture of cycloheptatriene (9·2 g., 0·1 mole), t-butyl chloride (9·3 g., 0·1 mole), and aluminium chloride (13·4 g., 0·05 mole) was heated under reflux with stirring under argon for 1 hr., and then cooled. Pentane (50 ml.) was added. The buff-coloured paste was filtered off, washed with pentane, and while still damp with pentane was quickly transferred to a Soxhlet apparatus. Extraction with ether for 14 hr. left a colourless solid. Last traces of ether were removed under reduced pressure to give the highly deliquescent *tropylium tetrachloroaluminate* (5·64 g., 22%), m. p. 208° (decomp.) (Found: C, 31·5; H, 3·7; Al, 10·1; Cl, 52·4. Calc. for $C_7H_7AlCl_4$: C, 32·3; H ,2·7; Al, 10·4; Cl, 54·6%. $C_7H_7AlCl_4$ containing 3% of H_2O requires C, 31·4; H, 3·0; Al, 10·1; Cl, 52·9%). The compound was freely soluble in water and ethanol, and insoluble in ether and hydrocarbons.

(b) *From tropylium chloride and aluminium chloride ethanolate.* A solution of aluminium chloride (1·3 g., 0·005 mole) in ethanol (30 ml.) was added with stirring at room temperature to a solution of tropylium chloride (1·26 g., 0·01 mole) in ethanol (20 ml.). The mixed solution was kept in a desiccator for 2 hr., and then ether (200 ml.) was added. By the procedure

[15] Doering and Knox, *J. Amer. Chem. Soc.*, 1957, **79**, 352.

described for the previous experiment, tropylium tetrachloroaluminate (1·78 g., 70%) was obtained. As in the previous case, the highly deliquescent nature of this material hindered accurate analysis (Found: C, 30·3; H, 3·5; Al, 10·2; Cl, 52·7. Calc. for $C_7H_7AlCl_4$, containing 6% of H_2O: C, 30·4; H, 3·2; Al, 9·8; Cl, 51·3%).

Preparation of Tropylium Tetrachloroferrate.—(a) *From cycloheptatriene, t-butyl chloride, and ferric chloride.* Ferric chloride (16·2 g.) was added with stirring to a mixture of cycloheptatriene (18·4 g.) and t-butyl chloride (19·0 g.). Hydrogen chloride was soon evolved, and the temperature was kept below 50° by cooling. When the evolution of heat ceased, the product was stirred at 65° for 5 hr. and then cooled. Pentane (50 ml.) was added and the whole product was transferred to a 100-ml. measuring cylinder. Unchanged ferric chloride rapidly settled and the supernatant yellow suspension was decanted. This procedure was repeated twice more. The final suspension was filtered and the yellow residue washed with ethanol (3 × 30 ml.) and finally with pentane.

Tropylium tetrachloroferrate (3·0g., 5%) was obtained as a yellow solid, m. p. 227° (Found: C, 29·5; H, 2·6; Cl, 48·6; Fe, 19·0. Calc. for $C_7H_7Cl_4Fe$: C, 29·1; H, 2·5; Cl, 49·1; Fe, 19·3%). The compound was stable in moist air, freely soluble in water and acetone, sparingly soluble in ethanol, and insoluble in ether and hydrocarbons.

(b) *From tropylium chloride and ferric chloride ethanolate.* A solution of ferric chloride (1·62 g., 0·005 mole) in ethanol (20 ml.) was added with stirring to a solution of tropylium chloride (1·26 g., 0·01 mole) in ethanol (50 ml.). After 1 hr. the yellow solid was filtered off, washed with ethanol (3 × 10 ml.) and then pentane, giving tropylium tetrachloroferrate (2·43 g., 84%), m. p. 228° (Found: C, 29·4; H, 2·7; Cl, 48·9; Fe, 19·2%).

Reaction of Cycloheptatriene, t-Butyl Chloride and Silicon Tetrachloride.—A mixture of the three components (9·2 g., 9·3 g., and 17·0 g., respectively) in hexane (50 ml.) was kept at 20° under nitrogen for 4 weeks. Traces of a brown solid separated. No pure compound was isolated, but the formation of a very small proportion of tropylium ions (0·07%) was recognised from the ultraviolet spectrum of a 2N-hydrochloric acid extract, and confirmed by the colour test with sodium tetraphenylboron.[8] A control experiment in which silicon tetrachloride was omitted gave no trace of tropylium ions.

A similar experiment with silicon tetrachloride was conducted for 12 days at 63°, and gave tropylium ions (0·03%).

Tropylium Pentachlorotitanate.—Analytical results for the products obtained by both of the following procedures are mediocre, and were obtained only with difficulty. A nitrogen atmosphere was maintained throughout each experiment.

(*a*) Titanium tetrachloride (56·8 g.) was added with stirring during 40 min. to a refluxing mixture of cycloheptatriene (55·2 g.), t-butyl chloride (55·6 g.), and hexane (400 ml.). The red-brown product was stirred under reflux for 5 hr. The buff precipitate was filtered off and washed with light petroleum (500 ml.; b. p. 40—60°). Drying *in vacuo* at 60° gave the *product* (22·35 g.) as a yellow powder, m. p. *ca.* 130° (decomp.: rather indefinite) [Found: C, 19·8; H, 2·3; Cl, 56·9; Ti, 16·4 (total 95·4%). $C_7H_7Cl_5Ti$ requires C, 26·6; H, 2·2; Cl, 56·1; Ti, 15·1%]. The tropylium ion content, estimated spectroscopically, was 25·1% (Calc. for $C_7H_7^+TiCl_5^-$: 28·8%). The low values for carbon were repeatedly confirmed (Drs. Weiler and Strauss, Oxford). The cause of the discrepancy is uncertain, but the presence of titanium may possibly have caused some interference. If the deficiency of 4·6% is assumed to be due to carbon, C : H = 0·9, which is much more in accord with the spectroscopic result than is the ratio 0·73 indicated without such correction. The structure $(C_7H_7)_2^{2+}TiCl_6^{2-}$ is ruled out (Calc. for $C_{14}H_{14}Cl_6Ti$: C, 37·9; H, 3·2; Cl, 48·0; Ti, 10·9; $C_7H_7^+$, 41·1%). (*b*) A mixture of tropylium chloride (1·35 g.) and titanium tetrachloride (7·3 g.) was kept at room temperature for 2 days with occasional shaking. Light petroleum (200 ml.; b. p. 60—80°) was then added. The yellow product (0·72 g.) was isolated as in the preceding experiment (Found: C, 27·1; H, 3·6; Cl, 52·8%). These values suggest that the product was contaminated with tropylium chloride, which has very similar solubility properties, and from which no complete separation could be devised. Spectroscopic determination of $C_7H_7^+$ gave the value 30·3%.

Di(cycloheptatrienyl) Ether.—Tropylium stannichloride (25·67 g.) was added steadily during 3 hr. to a well-stirred mixture of sodium hydrogen carbonate (42 g.), water (200 ml.), and pentane (100 ml.) at room temperature, and stirring was continued for a further 3 hr. Fractional distillation of the separated and dried ($MgSO_4$) pentane solution in alkali-washed apparatus gave di(cycloheptatrienyl) ether (6·56 g., 66%), b. p. 105—108°/0·7 mm. The

absence of cycloheptatrienone was demonstrated by the absence of any peak at 6·3 μ. The compound was stable in the dark under nitrogen at 140° in alkali-washed glass, but in acid-washed glass under these conditions, cycloheptatrienone and cycloheptatriene were slowly formed (ultraviolet and infrared spectra). Cycloheptatrienone 2,4-dinitrophenylhydrazone had m. p. 177° (lit., 176—177°,[16] 165—166° [11]) and the correct analysis.

The use of equivalent proportions of sodium carbonate and sodium hydroxide (allowing for the formation of sodium stannate) in place of sodium hydrogen carbonate in the above preparation led to yields of 51 and 45%, respectively.

We thank Dr. A. F. Bickel for communicating details of unpublished results, Koninklijke/Shell-Laboratorium, Amsterdam, for analytical assistance with the titanium complex, and Shell Research Ltd. for a maintenance grant (to N. A. P.) and gifts of chemicals.

CHEMISTRY DEPARTMENT, THE UNIVERSITY, READING, BERKS. [*Received, December 28th*, 1960.]

[11] Nozoe, Mukai, Takase, and Nagase, *Proc. Japan Acad.*, 1952, **28**, 477.

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450. *The Interaction of Phenylboronic Acid with Hexosides.*

By R. J. FERRIER.

Methyl α-D-glucopyranoside reacts with phenylboronic acid (1 mol.) to give a crystalline 4,6-cyclic ester which, in turn, forms a 2,3-(diphenylpyroboronate) (containing a 7-membered ring) with an excess of the reagent. Phenylboronic acid (2 mol.) condenses smoothly with methyl α-D-mannopyranoside, to give the 2,3:4,6-diester, but with 1 mol. of the acid this reaction does not give a homogeneous product. Substituted phenylboronate esters of methyl α-D-glucopyranoside, and phenylboronates of other glycosides and related compounds, are reported. All the derivatives described are air-stable solids which readily decompose in water or alcohols. The ester linkages have been shown to be stable to esterifying conditions but unstable during methylation.

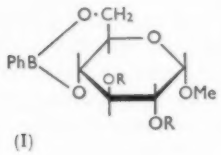
THE interaction in aqueous solution of boric acid with hydroxylated compounds has been studied extensively,[1] but less attention has been paid to the reactions which take place in non-aqueous solvents. The possibility of triester formation complicates the investigation of the cyclic borates formed from diols, and with carbohydrate derivatives, which concern us here, condensation, with dimerisation, of such diesters has been shown to occur.[2] In an attempt to overcome this difficulty, phenylboronic acid, which is known to condense with polyhydroxy-compounds to give cyclic esters,[3] has been used in model experiments. Some crystalline phenylboronates of hexitols [3] and free sugars [4] have already been reported, but little is known of the kinds of diol system with which the acid will react.

Although methyl α- and β-D-glucopyranoside have been found to react with both boric acid [5] and phenylboronic acid,[6] discrete esters have not been reported and the sites of esterification have not been well defined. We have examined the action of 1 mol. of phenylboronic acid on these glycosides, and by azeotropic distillation in the presence of benzene to remove water have been able to obtain crystalline cyclic esters in high yield. The anhydride of phenylboronic acid (triphenylboroxole) was equally effective in the syntheses.

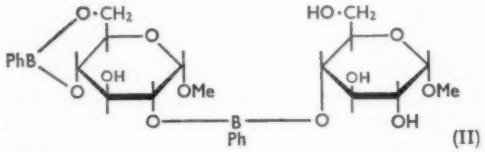
To determine the stability and sites of the boronate linkages, esterification and etherification of the free hydroxyl groups in the compounds were examined. Sugihara and

[1] For reviews see Böeseken, *Adv. Carbohydrate Chem.*, 1949, **4**, 189; Foster, *ibid.*, 1957, **12**, 81.
[2] Ferrier, unpublished results; cf. Gerrard, Lappert, and Mountfield, *J.*, 1959, 1529.
[3] Kuivila, Keough, and Soboczenski, *J. Org. Chem.*, 1954, **19**, 780.
[4] Wolfrom and Solms, *J. Org. Chem.*, 1956, **21**, 815.
[5] (*a*) Sugihara and Petersen, *J. Amer. Chem. Soc.*, 1956, **78**, 1760; (*b*) Bell, *J.*, 1935, 175.
[6] Sugihara and Bowman, *J. Amer. Chem. Soc.*, 1958, **80**, 2443.

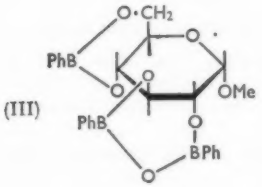
Bowman [6] found that the ester linkages of pyrogallol phenylboronate were stable towards benzoyl chloride in pyridine but unstable towards acetic anhydride in pyridine, as a mono-*O*-benzoate and a tri-*O*-acetate were produced. Smooth benzoylation (benzoyl



(I)



(II)



(III)

chloride in pyridine) and acetylation (acetyl chloride in pyridine) of methyl α-D-glucopyranoside phenylboronate yielded a crystalline di-*O*-benzoate and di-*O*-acetate which were, respectively, identical with the compounds (I; R = Bz, Ac) prepared by the action of phenylboronic acid on methyl α-D-glucoside 2,3-dibenzoate and 2,3-diacetate. The product of the initial reaction is therefore methyl α-D-glucopyranoside 4,6-phenylboronate (I; R = H). Thus two *trans*-fused six-membered ring systems (cf. methyl 4,6-*O*-benzylidene-α-D-glucopyranoside) have been formed.

Repeated unsuccessful attempts were made to prepare a crystalline product by the toluene-*p*-sulphonylation of the boronate (I; R = H), but the expected polyester (I; R = *p*-$C_6H_4Me{\cdot}SO_2$) was obtained by esterification of methyl 2,3-di-*O*-tosyl-α-D-glucopyranoside with phenylboronic acid.

The methyl ether (I; R = Me) was readily prepared from methyl 2,3-di-*O*-methyl-α-D-glucopyranoside and phenylboronic acid but was obtained only in poor yield on methylation of the phenylboronate (I; R = H) with methyl iodide and silver oxide. Chromatographic examination of the hydrolysed methylation products indicated that the boronate ring had ruptured during the reaction. Tri-*O*-methylglucose, together with the expected di-*O*-methylglucose, was detected in significant quantities after acid hydrolysis. No tetra-*O*-methylglucose could be found. Addition of desiccants to the methylation medium did not prevent cleavage of the ring. Obviously caution must be exercised in the interpretation of the results of methylation experiments involving borate esters.[5b]

All the boronates described are air-stable solids which crystallise readily from hydrocarbon solvents [but see methyl α-D-glucopyranoside 2,3-(diphenylpyroboronate) 4,6-phenylboronate]. On addition of water or alcohols to solutions in dry dioxan there is an immediate change in optical rotation. In each case the magnitude of the rotational change is consistent with the occurrence of B–O bond fission with retention of the sugar configuration and regeneration of the parent glycoside. Other borates and boronates have been shown to hydrolyse similarly [7] and, for example, Wolfrom and Solms [4] isolated L-arabinose from the hydrolysate of its di(phenylboronate).

The infrared spectra of the glycoside boronates are characterised by strong absorptions at 1350—1310 cm.$^{-1}$ which have been attributed [8] to the B–O stretching frequency, and much sharper ones at 1440 cm.$^{-1}$ arising from the B–aryl systems.[8]

[7] Lappert, *Chem. Rev.*, 1956, **56**, 959.
[8] Bellamy, Gerrard, Lappert, and Williams, *J.*, 1958, 2412.

Addition of triphenylboroxole to solutions in dioxan of the glycoside boronate (I; R = H) caused immediate changes in the optical rotations, but solutions of the 2,3-di-*O*-substituted derivatives were unaffected. As stated, alcohols (including cyclohexanol) cause the alcoholysis of the boronate rings. Consequently, it is possible that in solution the ester (I; R = H) might undergo intermolecular reaction to a slight extent, leading to compound (II) and related species. If the changes in rotation were due solely to interaction between the phenylboroxole and molecules of this type, or to changes in equilibria involving them, no effect would be observable in the benzylidene series but 2- and 3-mono-*O*-substituted derivatives of the ester (I; R = H) would be expected to be sensitive. The optical rotation of a solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was, however, markedly decreased by the addition of the boroxole, while its 2,3-di-*O*-substituted derivatives and methyl 2-deoxy-α-D-glycopyranoside 4,6-phenylboronate were unaffected. It is concluded that reaction occurs at, and requires, the *trans*-2,3-diol grouping.

Equimolecular amounts of phenylboronic acid and the ester (I; R = H) were heated in benzene [procedure (*a*)], and from the products approximately 50% of the boronate was recovered. Repetition of the condensation with 2 mol. of phenylboronic acid gave methyl α-D-glucopyranoside 2,3-(diphenylpyroboronate) 4,6-phenylboronate (III) which showed insignificant O–H stretching absorption in the infrared region. The similarity between the interactions of this reagent and acetaldehyde with methyl α-D-glucopyranoside becomes clear.[9]

The 7-membered ring formed is analogous, therefore, to that produced between phenylboronic acid and *trans*-cyclohexane-1,2-diol.[6,10] The compound recrystallised only when moisture was strictly excluded and the relative stabilities of the 6- and the 7-membered ring containing boron were demonstrated by partial hydrolysis of the fully esterified glycoside (III) to the disubstituted derivative (I; R = H) in wet benzene in good yield. The extreme instability of this 7-membered ring does not seem to be a general feature of such cyclic systems, as a compound analogous to the polyester (III) prepared from 1,5-anhydro-D-glucitol could be handled very readily and no product of partial hydrolysis was obtained on treatment with wet benzene.

From the above results and the observation that *cis*-cyclohexane-1,2-diol reacts smoothly to form a 5-membered boronate ring,[6] it was predicted that methyl α-D-mannopyranoside would yield a 2,3:4,6-di(phenylboronate). Reaction between this glycoside and phenylboronic acid did not occur in boiling benzene, but a hydroxyl-free ester was readily prepared in dioxan [2 mol. of acid; procedure (*b*)]. With 1 mol. of the reagent this glycoside gave rise to a syrup which slowly crystallised. No suitable method of purification was discovered, but condensation with more acid (1 mol.) gave the known crystalline di(phenylboronate). The partially substituted derivative was acetylated and after distillation the syrupy di-*O*-acetyl α-D-mannopyranoside phenylboronate consumed *ca.* 0·7 mol. of periodate. This result, together with the fact that analysis of the syrupy distillate indicated that it was contaminated with small amounts of acetolysed products, shows that phenylboronic acid combined with both the 4,6- and the 2,3-diol groupings of the glycoside, but preferably with the latter. It was shown that the phenylboronic acid liberated on treatment of the glycoside phenylboronates with aqueous periodate did not interfere with the course of the periodate oxidations.

Methyl β-D-galactopyranoside with phenylboronic acid (1 mol.) gives a discrete crystalline product. Preliminary investigations[11] indicate that this compound has the 4,6-cyclic structure.

Other compounds in this series are listed in the Table.

[9] Appel, Haworth, Cox, and Llewellyn, *J.*, 1938, 793.
[10] Compare the action of simple aldehydes on this compound: Head, *J.*, 1960, 1778.
[11] Ferrier, Hannaford, Overend, and Smith, unpublished results.

Phenylboronates and a diphenylpyroboronate.

Compound	Solvent for crystn.[a]	M. p.	$[\alpha]_D$	Found (%) C	H	B	Formula	Required (%) C	H	B
1	Benzene	188—189°	−82°	55·8	6·3	3·9	$C_{13}H_{17}BO_6$ [b]	55·7	6·1	3·9
2	Benzene	177—178	−91	63·7	6·0	3·0	$C_{19}H_{21}BO_6$	64·0	5·9	3·0
3	Benzene–Pet	142—143	+63	59·0	6·5	4·1	$C_{13}H_{17}BO_5$	59·1	6·4	4·1
4	Benzene	176—177	−80	57·0	6·1	4·2	$C_{12}H_{15}BO_5$	57·6	6·0	4·3
5	Pet	180—181	+265	60·6	4·7		$C_{18}H_{16}BNO_8$ [c]	61·2	4·6	
6	Benzene	164—165	+59	49·2	5·2	3·4	$C_{13}H_{16}BClO_6$ [d]	49·6	5·1	3·4
7	Benzene	168—169	+49	48·0	5·3	3·4	$C_{13}H_{16}BNO_8$ [e]	48·0	5·0	3·3
8	Benzene–Pet	188—189	−121	64·9	5·6	7·3	$C_{24}H_{23}B_3O_6$	65·4	5·3	7·4

Compounds (preparation procedure in parentheses): **1**, *methyl* β-D-*glucopyranoside* 4,6-*phenylboronate* (*a*); **2**, *benzyl* β-D-*glucopyranoside* 4,6-*phenylboronate* (*a*); **3**, *methyl* 2-*deoxy*-α-D-*glucopyranoside* 4,6-*phenylboronate* (*a*); **4**, 1,5-*anhydro*-D-*glucitol* 4,6-*phenylboronate* (*b*); **5**, p-*nitrophenyl* 2,3-*didehydro*-2,3-*dideoxy*-α-D-*glucopyranoside* 4,6-*phenylboronate* (*a*) (Ferrier, Overend, and Ryan, unpublished work); **6**, *methyl* α-D-*glucopyranoside* 4,6-p-*chlorophenylboronate* (*a*); **7**, *methyl* α-D-*glucopyranoside* 4,6-m-*nitrophenylboronate* (*a*); **8**, 1,5-*anhydro*-D-*glucitol* 2,3-(*diphenylpyroboronate*) 4,6-*phenylboronate* (*a*).

[a] Pet = light petroleum (b. p. 60—80°). [b] Found: MeO, 11·0. Reqd.: MeO, 11·1%. [c] Found: N, 4·0. Reqd.: N, 4·0%. [d] Found: Cl, 10·8. Reqd.: Cl, 11·3%. [e] Found: N, 4·3. Reqd.: N, 4·3%.

Experimental

The benzene and light petroleum used for recrystallisations of the boronates were dried over sodium wire. The specific rotations are quoted for 1% solutions in dioxan purified by fractional distillation from lithium aluminium hydride. They were measured in a 1 dm. tube at 22° ± 2°. It was shown that methoxyl determination by the infrared method of Anderson and Duncan [11] is satisfactory when applied to compounds containing boron. The author thanks Dr. D. M. W. Anderson (University of Edinburgh) for carrying out these analyses.

General Procedures for the Preparation of Boronate Esters (see Table).—(*a*) The reactants were stirred mechanically in boiling benzene, the water being collected in a Dean and Stark apparatus. The method gives quantitative yields, but is limited in that the water produced during small-scale reactions cannot be determined accurately. (*b*) The reactants were treated in boiling dioxan and the water produced was removed by careful fractional distillation of its azeotrope with the solvent. This method has two advantages over procedure (*a*): the compounds examined have a higher solubility in dioxan and this permits some reactions which do not proceed in benzene, and the water liberated in relatively small-scale experiments can be determined. For example, methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (0·3 g.) was boiled in dioxan (50 ml.) with an excess of triphenylboroxole; the total water of condensation was removed in about 10 ml. of distillate (column packed with glass helices and of about 20 theoretical plates), which was then diluted to 25 ml. with dry dioxan; 5 ml. aliquot parts of this solution were titrated by the Karl Fischer method; 1·0 mol. of water was found.

Methyl α-D-*Glucopyranoside* 4,6-*Phenylboronate*.—Methyl α-D-glucopyranoside (9·7 g.) and phenylboronic acid (6·1 g., 1 mol.) in benzene (1·2 l.) were treated according to procedure (*a*), and water (1·8 ml., 100% theor.) was collected. On cooling, crystals (10·0 g.) separated and further material (3·2 g., total 94%) was obtained on concentration of the filtrate. Sublimation, or recrystallisation from benzene, gave pure *methyl* α-D-*glucopyranoside* 4,6-*phenylboronate*, m. p. 166—167°, $[\alpha]_D$ +59° (Found: C, 56·0; H, 6·3; B, 3·9; OMe, 11·2%; *M*, 309. $C_{13}H_{17}BO_6$ requires C, 55·7; H, 6·1; B, 3·9; OMe, 11·1%; *M*, 280).

Methyl 2,3-*Di*-O-*benzoyl*-α-D-*glucopyranoside* 4,6-*Phenylboronate*.—To methyl α-D-glucopyranoside 4,6-phenylboronate (4·0 g.), dissolved in dry pyridine (30 ml.) at 0°, benzoyl chloride (4·0 ml.) was added slowly with stirring. Stirring was continued for 1 hr. at 0°, then the precipitated pyridine hydrochloride was removed and washed with hot benzene. The combined pyridine and benzene solutions were taken to dryness and the residue was extracted with hot benzene. Evaporation of this extract gave a syrup which crystallised readily on treatment with benzene–light petroleum (b. p. 60—80°). Recrystallisation from the same solvents yielded *methyl* 2,3-*di*-O-*benzoyl*-α-D-*glucopyranoside* 4,6-*phenylboronate* (4·4 g., 64%), m. p. 203—204°, $[\alpha]_D$ +94° (Found: C, 66·9; H, 4·8; B, 2·2; OMe, 6·3. $C_{27}H_{25}BO_8$ requires C, 66·4; H, 5·1; B, 2·2; OMe, 6·3%). The product obtained in quantitative yield from phenylboronic

[11] Anderson and Duncan, *Talanta*, 1960, **7**, 70.

acid and methyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside (0·006 mole) [procedure (*a*)] had m. p. 203—204° alone or on admixture with the above sample.

Methyl 2,3-*Di*-O-*acetyl*-α-D-*glucopyranoside* 4,6-*Phenylboronate*.—Methyl α-D-glucopyranoside 4,6-phenylboronate (2·0 g.) in dry pyridine (20 ml.) was treated with acetyl chloride (5·0 ml.). Working up as for the benzoyl derivative, followed by distillation, gave a pale yellow viscous syrup (1·7 g., 65%), b. p. 154°/0·17 mm., which crystallised completely on trituration with light petroleum (b. p. 60—80°). Recrystallisation from this solvent gave *methyl* 2,3-*di*-O-*acetyl*-α-D-*glucopyranoside* 4,6-*phenylboronate*, m. p. 116—117°, $[\alpha]_D$ +74° (Found: C, 56·6; H, 6·0; B, 2·9; OMe, 8·5. $C_{17}H_{21}BO_8$ requires C, 56·1; H, 5·8; B, 3·0; OMe, 8·5%). The m. p. on admixture with the compound (m. p. 115—116°) obtained in high yield by reaction of phenylboronic acid and methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside (0·01 mole) [procedure (*a*)] was 115—116°.

Methyl 2,3-*Di*-O-*tosyl*-α-D-*glucopyranoside* 4,6-*Phenylboronate*.—(*a*) Reaction of equimolecular amounts (0·005 mole) of phenylboronic acid and methyl 2,3-di-*O*-tosyl-α-D-glucopyranoside [procedure (*a*)] gave *methyl* 2,3-*di*-O-*tosyl*-α-D-*glucopyranoside* 4,6-*phenylboronate* in good yield; recrystallised from dry, alcohol-free chloroform–light petroleum (b. p. 60—80°), this had m. p. 180—181°, $[\alpha]_D$ −15° (Found: C, 55·5; H, 4·7; B, 1·8; OMe, 5·3; S, 11·0. $C_{27}H_{29}BO_{10}S_2$ requires C, 55·1; H, 5·0; B, 1·8; OMe, 5·3; S, 10·9%). (*b*) Toluene-*p*-sulphonyl chloride reacted with the glycoside phenylboronate (I; R = H) in dry pyridine, to liberate pyridine hydrochloride, but no crystalline glycoside derivative was obtained.

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopyranoside* 4,6-*Phenylboronate*.—(*a*) Methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (0·01 mole) and phenylboronic acid (0·01 mole) gave [procedure (*a*)] the 4,6-*phenylboronate* [from light petroleum (b. p. 60—80°)] in quantitative yield, with m. p. 119—121°, $[\alpha]_D$ +61° (Found: C, 58·7; H, 6·8; OMe, 29·6; B, 3·5. $C_{15}H_{21}BO_6$ requires C, 58·5; H, 6·9; OMe, 30·2; B, 3·5%). (*b*) Methyl α-D-glucopyranoside 4,6-phenylboronate (2·0 g.) was heated under reflux in methyl iodide (50 ml.) with silver oxide (3·0 g.) for 6 hr. The solids were removed and the solvent evaporated. Chromatographic analysis of the hydrolysate (2N-hydrochloric acid at 100° for 2 hr.) of the syrupy residue revealed mixtures of tri-, di-, and mono-*O*-methylglucose. The tri-*O*-methyl ethers were present in considerable quantity. Three successive such methylations resulted in increased amounts of di- and tri-*O*-methylglucose and less mono-*O*-methyl ether in the hydrolysate. No tetra-*O*-methylglucose could be detected. Addition of calcium chloride or Drierite to the methylation mixtures caused no observable change in products. The syrup obtained after one methylation of the boronate (4·0 g.) with methyl iodide (100 ml.) and silver oxide (12 g.) in the presence of Drierite (10 g.) was distilled. Redistillation of the crude product gave a viscous syrup from which crystals (0·1 g.) were obtained on trituration with light petroleum (b. p. 60—80°). Recrystallisation from this solvent gave methyl 2,3-di-*O*-methyl-α-D-glucopyranoside 4,6-phenylboronate, m. p. 120—122°, identical (mixed m. p.) with the product of reaction (*a*).

Methyl α-D-*Glucopyranoside* 2,3-(*Diphenylpyroboronate*) 4,6-*Phenylboronate*.—Methyl α-D-glucopyranoside 4,6-phenylboronate (6·7 g.) and triphenylboroxole (2·5 g., 0·33 mol.) were caused to react by procedure (*a*) (700 ml. of benzene); water was eliminated. Unchanged ester (3·1 g., 46%) was recovered and was the only crystalline material obtained. The condensation was repeated [procedure (*b*)] with double quantity of triphenylboroxole. Removal of the dioxan gave, in quantitative yield, a product which crystallised on trituration with light petroleum (b. p. 60—80°; dried by lithium aluminium hydride), m. p. 161—163°. Recrystallisation from the same solvent gave *methyl* α-D-*glucopyranoside* 2,3-(*diphenylpyroboronate*) 4,6-*phenylboronate*, m. p. 162—163°, $[\alpha]_D$ −31° (Found: C, 64·0; H, 5·5; B, 6·8. $C_{25}H_{25}B_3O_7$ requires C, 63·9; H, 5·4; B, 6·9%). All samples studied had slight O–H stretching absorptions in the infrared region, but the magnitudes of these absorptions indicated that the molecular structure was devoid of hydroxyl groupings. The spectrum of the analogous compound derived from 1,5-anhydro-D-glucitol (see Table 1) lacked absorption in this region.

The polyester (10 g.) was dissolved in benzene (250 ml.), water (0·8 ml.) was added, and the mixture was shaken. Overnight precipitation occurred of methyl α-D-glucopyranoside 4,6-phenylboronate (4·7 g., 79%), m. p. and mixed m. p. 166—167°, $[\alpha]_D$ +60°.

Methyl α-D-*Mannopyranoside Phenylboronate*.—Methyl α-D-mannopyranoside (2·0 g.) with phenylboronic acid (1·2 g., 1 mol.) [procedure (*b*)] gave a syrup (2·8 g.) which slowly crystallised. The solid was insoluble in benzene and no suitable solvent for recrystallisation could be found;

it had m. p. (after draining on porcelain tile) 106—108°, $[\alpha]_D$ −52° (Found: C, 56·6; H, 6·1; B, 3·9. $C_{13}H_{17}BO_6$ requires C, 55·7; H, 6·1; B, 3·9%). Treatment of this solid (0·2 g.) with phenylboronic acid (0·09 g., 1 mol.) yielded *methyl* α-D-*mannopyranoside* 2,3:4,6-*di*(*phenylboronate*) (0·16 g., 60%), m. p. 112—115°; recrystallised from light petroleum (b. p. 60—80°) it had m. p. 116—117°, $[\alpha]_D$ −118°, devoid of OH infrared absorption (Found: C, 61·9; H, 5·6; B, 5·8. $C_{19}H_{20}B_2O_6$ requires C, 62·3; H, 5·5; B, 5·9%). This compound had undepressed m. p. on admixture with that readily obtained from methyl α-D-mannopyranoside and 2 mol. of phenylboronic acid [procedure (*b*)].

The methyl α-D-mannopyranoside phenylboronate (2·6 g.) was acetylated under the conditions used to prepare methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside 4,6-phenylboronate, to give a syrup (2·5 g., 74%) part of which (0·6 g.) was distilled. The resulting glassy *product* (0·35 g.), $[\alpha]_D$ −5·4°, consumed 0·73 mol. of periodate (see below) (Found: C, 55·6; H, 6·0; Ac, 27·0; B, 2·8. $C_{17}H_{21}BO_8$ requires C, 56·1; H, 5·8; Ac, 23·6; B, 3·0%).

Periodate Oxidation of Glycoside Boronates.—The oxidations were carried out with aqueous sodium metaperiodate containing dioxan (5%) (added initially to dissolve the esters). The consumption of reagent was followed spectrophotometrically,[13] any absorptions due to the esters or solvent being nullified by incorporation of these in the blank cells.

Results. Consumptions of periodate were: methyl α-D-glucopyranoside 4,6-phenylboronate 1·95 mol. (5 hr. const.); methyl α-D-mannopyranoside 2,3:4,6-di(phenylboronate) 1·95 mol. (5 hr. const.); methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside 4,6-phenylboronate, no uptake during 3 days; methyl di-*O*-acetyl-α-D-mannopyranoside phenylboronate 0·73 mol. (5 hr. const.).

The author thanks Professor W. G. Overend for his interest and advice, Dr. B. C. Smith for much helpful discussion and for molecular-weight determinations, and Dr. W. J. Rosenfelder of Borax Consolidated, Ltd., for a gift of phenylboronic acids.

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[13] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.

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451. *Triterpene Constituents of the Fruits of the Osage Orange* (Maclura pomifera). *Part II.*[1] *Synthesis of the Natural Diol, Lupane-3β,20-diol.*

By K. G. LEWIS.

The structure, lupane-3β,20-diol, previously proposed for a new triterpene isolated from the fruits of the osage orange, has been confirmed by the identity of the natural material with this diol formed by reduction of lupenyl acetate epoxide.

EVIDENCE presented in Part I [1] pointed to the structure lupane-3β,20-diol (I; R = H) for a new triterpene diol isolated from the fruits of the osage orange. Neither this diol (I) nor the possible alternative, 18α-oleanane-3β,19α-diol (II; R = H), had been observed to occur in Nature before. Chatterjee, Anand, and Dhar [2] later assigned the structure lupane-3,20-diol to a compound, m. p. 232°, $[\alpha]_D$ +24°, previously isolated [3] from *Melodinus monogynus* Roxb. Their evidence was dehydration of the diol to lupeol on vacuum-sublimation and conversion of the diol into lupenyl acetate by boiling acetic anhydride. The m. p. recorded by them is in fair agreement with that found for the osage orange diol, but the rotation differs considerably. No further derivatives of the material from *Melodinus monogynus* were reported.

A substance of structure (II) had been reported by Ames, Davey, Halsall, and Jones [4] and the m. p. of the monoacetate (II; R = Ac) agreed quite well with that of the osage

[1] Part I, Lewis, *J.*, 1959, 73.
[2] Chatterjee, Anand, and Dhar, *J. Sci. Ind. Res., India*, 1959, **18***B*, 262.
[3] Chatterjee, Sharma, and Dhar, *J. Sci. Ind. Res., India*, 1954, **13***B*, 546.
[4] Ames, Davey, Halsall, and Jones, *J.*, 1952, 2868.

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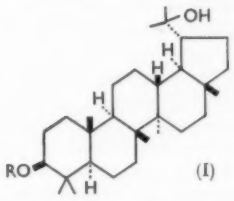
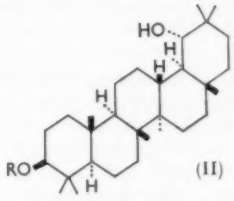
orange derivative. The two substances, however, showed a substantial mixed m. p. depression and their infrared spectra showed appreciable differences. The correctness of structure (I) was finally proved by synthesis of a substance having this structure, by reduction of lupenyl acetate epoxide with lithium aluminium hydride. The lithium aluminium hydride cleavage of primary-tertiary and secondary-tertiary epoxides is known [5]



(I)



(II)

to give the tertiary alcohol (a parallel case is the reduction of thurberogenin epoxide [6]). The synthetic diol and its derivatives were identical with the material from osage orange and its derivatives.

The parent diol, lupane-3β,20-diol, was fairly easily dehydrated. While the monoacetate and monobenzoate could be dried for analysis for some hours at *ca.* 80°/0·01 mm., the diol under similar conditions gave material of lowered m. p. Acetylation of the vacuum-dried material, followed by chromatography, afforded lupenyl acetate as well as the diol monoacetate (I; R = Ac). In the benzoylation of the diol some elimination also occurred, as lupenyl benzoate was isolated as well as the monobenzoate.

Experimental

Specific rotations were determined for chloroform solutions. "Light petroleum" refers to the fraction of b. p. 40—60°. Alumina was Woelm's material deactivated by addition of 3% of 10% acetic acid (activity II—III). Infrared absorption spectra were determined for Nujol mulls.

Isolation of Lupane-3β,20-diol 3-Monoacetate (I; R = Ac) *from Osage Orange.*—Crude diol isolated as described in Part I [1] was treated with pyridine–acetic anhydride overnight. The mixed acetates were chromatographed in light petroleum over alumina. Light petroleum eluted mainly lupenyl acetate; benzene–light petroleum yielded the diol monoacetate, m. p. 252—255° (needles from methanol–chloroform), $[\alpha]_D$ +16° (*c* 2·52) (Found: C, 79·1; H, 11·2. Calc. for $C_{32}H_{54}O_3$: C, 79·0; H, 11·2%). Hydrolysis of this acetate with potassium hydroxide or reduction with lithium aluminium hydride yielded *lupane-3β,20-diol* as needles, m. p. 239—241° (from acetone), $[\alpha]_D$ +4° (*c* 2·21) (Found: C, 81·5; H, 11·8; O, 7·3. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8; O, 7·2%). After being dried at 90°/0·01 mm. for 7 hr. it had m. p. 195—205°. The dried material was acetylated and the mixture of acetates separated by chromatography over alumina, to yield lupenyl acetate, m. p. and mixed m. p. 211—213°, and the diol monoacetate, m. p. 250—254°, giving no depression with the original diol monoacetate. The diol and pyridine–benzoyl chloride at room temperature overnight gave a product which was chromatographed over alumina. Elution with light petroleum gave lupenyl benzoate, m. p. and mixed m. p. 265—268° (from methanol–chloroform), $[\alpha]_D$ +58° (*c* 2·25) (Found: C, 83·4; H, 10·1. Calc. for $C_{37}H_{54}O_2$: C, 83·7; H, 10·25%). Elution with benzene–light petroleum (1 : 1) yielded *lupane-3β,20-diol 3-monobenzoate*, m. p. 253—256° (hexagonal plates from methanol–chloroform), $[\alpha]_D$ +35° (*c* 2·49) (Found: C, 80·9; H, 10·4. $C_{37}H_{56}O_3$ requires C, 81·0; H, 10·3%).

Preparation of 18α-Oleanane-3β,19α-diol 3-Monoacetate (II; R = Ac).—The procedure outlined by Ames *et al.*[4] afforded the monoacetate, m. p. 248—251° (needles from methanol–chloroform), $[\alpha]_D$ +6° (*c* 2·28) (Found: C, 78·85; H, 10·9. Calc. for $C_{32}H_{54}O_3$: C, 79·0; H,

[5] Micovic and Mihailovic, "Lithium Aluminium Hydride in Organic Chemistry," Serbian Academy of Sciences, Belgrade, 1955, p. 69.

[6] Djerassi, Liu, Farkas, Lippman, Lemin, Geller, McDonald, and Taylor, *J. Amer. Chem. Soc.*, 1955, **77**, 1200.

11·2%). Ames *et al.*[4] record m. p. 249—250°, $[\alpha]_D$ +7°. A mixed m. p. determination with osage orange diol monoacetate gave m. p. 215—230°.

Lupenyl Acetate Epoxide.—Lupenyl acetate, in chloroform, was treated with monoperphthalic acid in ether. Titration indicated that the reaction was complete within 3 hr. The solution was poured into water and the epoxide extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate and water. Lupenyl acetate epoxide had m. p. 235—238° (from acetone), $[\alpha]_D$ +23° (*c* 2·36) (Found: C, 79·7; H, 10·6; O, 9·5. Calc. for $C_{32}H_{52}O_3$: C, 79·3; H, 10·8; O, 9·9%). Ruzicka and Rosenkranz [7] record m. p. 226—230°, $[\alpha]_D$ +24°.

Partial Synthesis of Lupane-3β,20-diol 3-Monoacetate.—Lupenyl acetate epoxide was added in dry ether to an excess of lithium aluminium hydride in dry ether. The mixture was refluxed for 16 hr. and the excess of lithium aluminium hydride then destroyed by ethyl acetate. Water and hydrochloric acid were then added and the mixture was extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate and water and the extract dried. Evaporation yielded a white solid which was treated with pyridine–acetic anhydride at room temperature overnight. Working up yielded material which on chromatography over alumina yielded the diol monoacetate, m. p. 250—253° (from methanol–chloroform), $[\alpha]_D$ +16° (*c* 2·46) (Found: C, 78·7; H, 11·0%). This material gave no m. p. depression on admixture with the diol monoacetate from osage orange, and the infrared spectra were identical.

Lupane-3β,20-diol 3-Monobenzoate.—Hydrolysis of the above monoacetate yielded crude diol which was treated with pyridine–benzoyl chloride overnight. Working up yielded material which was chromatographed over alumina. Elution with light petroleum removed an oil and further elution with benzene–light petroleum yielded the diol monobenzoate, m. p. 254—256°, $[\alpha]_D$ +35° (*c* 2·47) (Found: C, 81·25; H, 10·2. Calc. for $C_{37}H_{56}O_3$: C, 81·0; H, 10·3%). There was no m. p. depression on admixture with the diol monobenzoate from osage orange, and the infrared spectra were identical.

Lupane-3β,20-diol.—Lupenyl acetate epoxide was reduced with lithium aluminium hydride in tetrahydrofuran (cf. Djerassi *et al.*[6]) to yield lupane-3β,20-diol, m. p. 238·5—241° (from acetone), $[\alpha]_D$ +5·5° (*c* 2·24). There was no depression on mixed m. p. with osage orange diol. Both samples of diol gave identical *X*-ray powder photographs.

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[7] Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1939, **22**, 778.

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452. *π-Complexes of Biphenylene.*

By J. CHATT, R. G. GUY, and H. R. WATSON.

Biphenylene readily forms co-ordination compounds using one or both of its six-membered rings, but not its four-membered ring.

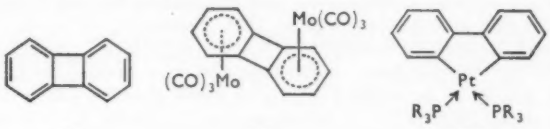
BIPHENYLENE can be written with five Kekulé structures of which one represents it as a cyclobutane derivative (I), two as a cyclobutadiene derivative, and the remaining two as a cyclobutene derivative. In might therefore be expected to form co-ordination compounds by using either of its six-, or its four-membered ring. We have attempted to obtain both types of complex but succeeded in getting only the benzene type.

When biphenylene is heated at 130° for 4 hr. with tricarbonyldiglymemolybdenum (4 mols.) [diglyme = $O(CH_2{\cdot}CH_2{\cdot}OMe)_2$] it readily forms scarlet μ-biphenylenebis(tricarbonylmolybdenum) (II). The *trans*-arrangement is implied from the molecular centre of symmetry shown by the *X*-ray crystal data. This substance is stable in air and only sparingly soluble in hot organic solvents, giving solutions which rapidly decompose. Equimolecular proportions of the above reactants, heated at 100° for 6½ hr., form orange tricarbonylbiphenylenemolybdenum, $[C_{12}H_8Mo(CO)_3]$, soluble in organic solvents.

Its solutions slowly deposit molybdenum. The biphenylene can be recovered from both products by reaction with 1,2-bis(diphenylphosphino)ethane:

$$[C_{12}H_8\{Mo(CO)_2\}_n] + 2nC_2H_4(PPh_2)_2 \longrightarrow C_{12}H_8 + n[Mo(CO)_2\{C_2H_4(PPh_2)_2\}_2] + nCO$$
$$(n = 1 \text{ or } 2)$$

To see whether the 4-membered ring of biphenylene has sufficient cyclobutadienoid character to react with compounds of metals near the end of the transition series to form such complexes as [$Fe(CO)_3$(biphenylene)], [$Ni(CO)_2$(biphenylene)], [Ni(biphenylene)$_2$], or [Pt(biphenylene) (PR_3)$_2$] we treated biphenylene with compounds of iron, nickel, and platinum.[1] The iron compound, if it had been obtained, would have been exactly analogous to [$Fe(CO)_3$(tetraphenylcyclobutadiene)].[2]



(I) (II) (III)

No complex was detected on treating biphenylene with (*a*) $Fe(CO)_5$, (*b*) $Ni(CO)_4$, (*c*) [$Ni(CO)_3(PPh_3)$], or (*d*) nickelocene, $Ni(C_5H_5)_2$, under the conditions given in the Table. However, when biphenylene was treated with [$Ni(CO)_2(PPh_3)_2$] in a sealed tube at 100°, it gave a small yield of tetraphenylene (1,2:3,4:5,6:7,8-tetrabenzocyclo-octatetraene). This dimerisation may have proceeded through the formation of a biphenylene complex, since it has been suggested [3] that a nickel complex of cyclobutadiene is involved in the analogous formation of cyclo-octatetraene from acetylene.

Attempts to obtain platinum complexes were equally unsuccessful. Biphenylene did not react with *cis*-[$PtCl_2(PPh_3)_2$] and hydrazine [4] to form a complex of the type [Pt(biphenylene)(PR_3)$_2$]. Attempts to prepare this type of complex from *cis*-[$PtCl_2(PR_3)_2$] and 2,2′-dilithiobiphenyl or related Grignard reagents (prepared from 2,2′-di-iodobiphenyl) gave products of the type *trans*-[$PtIR'(PR_3)_2$],[5] where R′ is 2-biphenylyl or 2,2′-iodobiphenylyl. It is interesting that the heterocyclic compound (III) was not obtained.

Reactions of biphenylene with iron, nickel, and platinum complexes.

Reagent Formula	Mol.	Conditions *	Substances isolated
$Fe(CO)_5$	5	Benzene soln./80°/250 w u.v. light/20 hr.	Biphenylene
$Ni(CO)_4$	2	Petrol soln./40°/3 hr.	Biphenylene
,,	4	Sealed tube/140°/12 hr.	,,
$Ni(CO)_2(PPh_3)$	1	100°/1 hr. or 16 hr.	Biphenylene, [$Ni(CO)_3(PPh_3)_2$]
$Ni(CO)_2(PPh_3)_2$	1	Benzene soln. in sealed tube/100°/1 hr.	Biphenylene
,,	1	Benzene soln. in sealed tube/100°/7 hr.	Tetraphenylene
$Ni(C_5H_5)_2$	1	Petrol soln./20°/5 days	Biphenylene
,,	0·5	,, ,,	,,
,,	0·5	,, 80°/21 hr.	,,
,,	4	150—160°/1·5 hr.	Biphenylene; & black solid †
cis-[$PtCl_2(PPh_3)_2$] and N_2H_4,H_2O	0·5	Ethanol soln. at 20°	Biphenylene

* All under nitrogen. † This solid, m. p. 350°, appears to be polymerised nickelocene [Found: C, 64·0; H, 5·05. Calc. for $(C_{10}H_{10}Ni)_n$: C, 63·6; H, 5·35%].

The capacity of biphenylene to form co-ordination compounds using each six-membered ring independently, but not the four-membered ring system, is consistent with the preferred

[1] For a preliminary account of this work see *Chem. Soc. Special Publ.* No. 12, 1958, p. 65.
[2] Dodge and Schomaker, *Nature*, 1960, **186**, 798.
[3] Longuet-Higgins and Orgel, *J.*, 1956, 1969.
[4] Cf. Chatt, Rowe, and Williams, *Proc. Chem. Soc.*, 1957, 208.
[5] Cf. Chatt and Shaw, *J.*, 1959, 4020.

XUM

bond structure (I),[6] in which there is little or no cyclobutadienoid character in the 4-membered ring.

Experimental

M. p.s were determined on a Kofler hot-stage and are corrected, except those marked with an asterisk which were taken in a nitrogen-filled tube.

Biphenylene was prepared by the method of Baker, Boarland, and McOmie,[7] and had m. p. 112—113°.

The following experiments were carried out under nitrogen.

μ-Biphenylenebis(tricarbonylmolybdenum).—Biphenylene (0·152 g.) and diglymemolybdenum tricarbonyl [8] (0·628 g.) were heated together at 130° for 4 hr.; molybdenum carbonyl sublimed from the fused red mass. The cooled mass was crushed coarsely and extracted with boiling " AnalaR " chloroform (5 × 5 ml.), the hot chloroform then being decanted. This operation removed all the finely divided molybdenum, and there remained the *bis(tricarbonyl)*, m. p.* 204° with prior shrinking and loss of colour at 195° [Found: C, 41·8; H, 1·75; Mo, 37·5%; *M* (by *X*-ray method, density by flotation), 510 ± 5. $C_{18}H_8Mo_2O_6$ requires C, 42·2; H, 1·6; Mo, 37·5%; *M*, 512·2]. Crystal data: monoclinic $2/m$, $a = 10·03 \pm 0·05$, $b = 11·52 \pm 0·06$, $c = 7·41 \pm 0·03$ Å, $\beta \approx 90·0°$, $U = 856·2$ Å^3, $D_M = 1·980 \pm 0·005$, $ZM = 1021 \pm 10$, $Z = 2$, $D_O = 1·974$, space group $P2_1/c$ (C_{2h}^5, No. 14), molecular symmetry $\bar{1}$. The infrared spectrum has carbonyl stretching bands at 1961 ± 2vs broad, 1942vs, 1923vs, and 1887 ± 2vs broad cm.$^{-1}$. The spectrum due to biphenylene is considerably altered; in particular the broad complex band centred on 734 cm.$^{-1}$ is missing.

A mixture of the bistricarbonyl (0·050 g.) and an excess of 1,2-bis(diphenylphosphino)ethane was heated rapidly from 60° to 140° at 0·05 mm. Biphenylene (0·012 g., 81%) sublimed, and *cis*-dicarbonyldi-1,2-bis(diphenylphosphino)ethanemolybdenum [9] (about 0·005 g.) was extracted from the black residue with acetone.

Biphenylenetricarbonylmolybdenum.—Biphenylene (0·235 g.) and diglymemolybdenum tricarbonyl (0·486 g.) were heated together at 100—103° for 6½ hr. The resulting red-brown mass crystallised from light petroleum (40—60°) to give the *tricarbonyl* (0·111 g., 21·5%), orange needles, m. p.* 163—185° (decomp.) (Found: C, 54·35; H, 2·55%; *M*, ebullioscopic in chloroform, 330. $C_{15}H_8O_3Mo$ requires C, 54·2; H, 2·4%; *M*, 332). The infrared spectrum has carbonyl stretching bands at 1967vs and 1878vs broad cm.$^{-1}$. The portion of the spectrum due to biphenylene is simpler than in the hydrocarbon; the broad band centred on 734 cm.$^{-1}$ is replaced by a sharp band at 752s cm.$^{-1}$. When heated with an excess of 1,2-bis(diphenylphosphino)ethane the compound (0·010 g.) gave biphenylene (0·0030 g.).

Reaction of Biphenylene with $[Ni(CO)_2(PPh_3)_2]$.—Biphenylene (0·10 g., 1 mol.), $[Ni(CO)_2(PPh_3)_2]$ (0·42 g., 1 mol.), and benzene (1·0 ml.) were heated in an atmosphere of nitrogen at 100° in a sealed tube. The clear yellow solution became brown after 3 hr., and was heated for a further 4 hr. After evaporation of the solvent, the yellow-green solid (0·52 g.) was treated with ethanol. The insoluble material was unchanged $[Ni(CO)_2(PPh_3)_2]$ (0·35 g.), m. p. and mixed m. p. 207—210° (decomp.). The ethanol-soluble portion was a sticky solid (0·16 g.); this was washed with light petroleum (b. p. 40—60°), and the residual light yellow solid (0·10 g.), on crystallisation from ethanol, gave 1,2:3,4:5,6:7,8-tetrabenzocyclo-octatetraene (tetraphenylene) as white prisms, m. p. 232—235° (Found: C, 94·9; H, 5·3. Calc. for $C_{24}H_{16}$: C, 94·7; H, 5·3%). Rapson, Shuttleworth, and van Niekerk [10] report m. p. 233°.

Reaction of 2,2′-Dilithiobiphenyl with cis-$[PtCl_2(PEt_3)_2]$.—The dilithio-compound was prepared under nitrogen in ether (25 ml.) from 2,2′-di-iodobiphenyl (1·02 g., 1 mol.) and lithium (0·09 g., 5 g.-atom).[11] A suspension of *cis*-$[PtCl_2(PEt_3)_2]$ (1·25 g., 1 mol.) in ether (10 ml.) was added and the mixture stirred at room temperature for 3 hr. The solution was filtered and evaporation of the filtrate yielded a brown solid which on recrystallisation from ethanol gave *[iodo-(2-biphenylyl)bis(triethylphosphine)platinum*(II)] (0·40 g.) as colourless plates, m. p. 190—195° (Found: C, 40·5; H, 5·55. $C_{24}H_{39}IP_2Pt$ requires C, 40·5; H, 5·5%). The dipole moment (3·0 ± 0·2 D) of this compound shows that it has the *trans*-configuration.[5,12]

[6] Baker, McOmie, Preston, and Rogers, *J.*, 1960, 414.
[7] Baker, Boarland, and McOmie, *J.*, 1954, 1476.
[8] Werner and Coffield, *Chem. and Ind.*, 1960, 936.
[9] Chatt and Watson, unpublished result.
[10] Rapson, Shuttleworth, and van Niekerk, *J.*, 1943, 326.
[11] Wittig and Herwig, *Chem. Ber.*, 1954, **87**, 1511.
[12] Cf. Chatt and Shaw, *J.*, 1959, 705.

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Reaction of the Mono-Grignard Reagent of 2,2′-Di-iodobiphenyl with cis-$[PtCl_2(PEt_3)_2]$.—Magnesium (0·12 g., 2 mol.) in ether (30 ml.) was treated with 2,2′-di-iodobiphenyl (1·02 g., 1 mol.), and the mixture heated under reflux in an atmosphere of nitrogen for 6 hr.[10] *cis*-$[PtCl_2(PEt_3)_2]$ (1·25 g., 1 mol.), suspended in ether (20 ml.), was added and the mixture stirred overnight at room temperature. Dilute hydrochloric acid was then added slowly, with ice-cooling. The insoluble material (0·28 g.) was collected, and on recrystallisation from benzene afforded pale yellow prisms of trans-[*iodo*-(2,2′-*iodobiphenylyl*)*bis*(*triethylphosphine*)*platinum*(II)], m. p. 270—275° (Found: C, 34·4; H, 4·55. $C_{24}H_{38}I_2P_2Pt$ requires C, 34·4; H, 4·55%). The rather high dipole moment (5·3 ± 0·1 D) indicates that some of the *cis*-isomer may be present. The residue from evaporation of the dried ($MgSO_4$) ether layer afforded *trans*-$[PtI_2(PEt_3)_2]$, m. p. and mixed m. p. 136—137°.

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453. *The Relationship of Structure to Activity in Plant Growth-regulating Compounds. Part I. Rates of Alkaline Hydrolysis of Substituted 2,4-Dichlorophenoxyacetamides.*

By A. M. Johnston.

A number of *N*-substituted 2,4-dichlorophenoxyacetamides have been prepared. The rates of hydrolysis of these compounds by 0·22N-alcoholic alkali have been determined. In this way these compounds can be ranked in order of chemical stability and according to the electron availability on the carbon atom of the amide group, which is the point of attack of the hydroxyl ion during hydrolysis.

In the course of an investigation into the plant growth-regulating activities of various derivatives of 2,4-dichlorophenoxyacetic acid it was noted that certain closely related *N*-substituted amides show considerable variation in plant growth-regulating activity. Wain and his co-workers [1] consider that the amides of active plant-growth regulating acids are not active as such but are first hydrolysed in the plant to the free acid. If this should be the case there will be a correlation between the rates of hydrolysis within the plant and the growth-regulating activities of the compounds. The mechanism and rate of hydrolysis, within the plant, of foreign substances is difficult to establish. As a preliminary measure of the chemical stability of such compounds, the rates of alkaline hydrolysis of a number of *N*-substituted 2,4-dichlorophenoxyacetamides were determined.

Experimental

Preparation of the Amides.—The amides were prepared by standard methods as follows.

Method 1. Recrystallised 2,4-dichlorophenoxyacetic acid was heated with a 50% molar excess of amine at 150—160° until evolution of water ceased. The excess of amine was removed by dilute hydrochloric acid and the product was crystallised.

Method 2. The appropriate amine was treated with 2,4-dichlorophenoxyacetyl chloride in the presence of a small excess of aqueous base.

Method 3. *N*-Methyl-*N*-phenyl-2,4-dichlorophenoxyacetamide (16) was prepared by methylating 2,4-dichlorophenoxyacetanilide with methyl iodide in acetone by Pachter and Kloetzel's method.[2]

[1] Wain and Wightman (Ed.), "The Chemistry and Mode of Action of Plant Growth Substances," Butterworths, London, 1956, pp. 187, 234.
[2] Pachter and Kloetzel, *J. Amer. Chem. Soc.*, 1952, **74**, 1321.

Method 4. The amino-anilides (10 and 11) were prepared by hydrogenating the corresponding nitroanilides over Raney nickel in dioxan at room temperature and pressure.

The following 2,4-dichlorophenoxyacetamides were prepared by these methods: (1) 2,4-Dichlorophenoxyacetamide,[3] method 2, needles, m. p. 155° (Found: N, 6·2. Calc. for $C_8H_7Cl_2NO_2$: N, 6·4%). (2) N-*Methyl*, method 2, needles, m. p. 110—110·5° (Found: C, 46·1; H, 3·9. $C_9H_9Cl_2NO_2$ requires C, 46·2; H, 3·9%). (3) N-*Ethyl*, method 2, needles, m. p. 108—108·5° (Found: C, 48·4; H, 4·4. $C_{10}H_{11}Cl_2NO_2$ requires C, 48·4; H, 4·4%). (4) N-*Isopropyl*, method 2, needles, m. p. 125—125·5° (Found: C, 50·4; H, 4·8. $C_{11}H_{13}Cl_2NO_2$ requires C, 50·4; H, 5·0%). (5) *N*-2′-Hydroxyethyl,[4] method 2, needles, m. p. 121·5—122·5° (Found: C, 45·2; H, 4·05. Calc. for $C_{10}H_{11}Cl_2NO_3$: C, 45·5; H, 4·2%). (6) *N*-Phenyl,[5] method 1, needles, m. p. 109—110° (Found: N, 4·6. Calc. for $C_{14}H_{11}Cl_2NO_2$: N, 4·7%). (7) N-p-*Tolyl*, method 1, needles, m. p. 140·5° (Found: N, 4·3. $C_{15}H_{13}Cl_2NO_2$ requires N, 4·5%). (8) *N*-*p*-Nitrophenyl,[6] method 1, plates, m. p. 202—203·5° (Found: C, 49·6; H, 3·0. Calc. for $C_{14}H_{10}Cl_2N_2O_4$: C, 49·3; H, 2·9%). (9) N-m-*Nitrophenyl*, method 1, needles, m. p. 200—201° (Found: C, 49·2; H, 3·0%). (10) *N*-*p*-Aminophenyl,[6] method 4, needles, m. p. 140—143° (Found: C, 53·9; H, 3·9. Calc. for $C_{14}H_{12}Cl_2N_2O_2$: C, 54·0; H, 3·9%). (11) N-m-*Aminophenyl*, method 4, needles, m. p. 132·5—135° (Found: C, 53·9; H, 3·9%). (12) N-p-*Chlorophenyl*, method 2, needles, m. p. 155·5—156° (Found: C, 50·7; H, 3·1. $C_{14}H_{10}Cl_3NO_2$ requires C, 50·8; H, 3·0%). (13) N-3,4-*Dichlorophenyl*, method 2, needles, m. p. 166·5—167° (Found: C, 45·9; H, 2·5. $C_{14}H_9Cl_4NO_2$ requires C, 46·0; H, 2·5%). (14) N,N-*Dimethyl*, method 2, needles, m. p. 110·5—111·5° (Found: C, 48·0; H, 4·5. $C_{10}H_{11}Cl_2NO_2$ requires C, 48·4; H, 4·4%). (15) NN-*Bis*-2-*hydroxyethyl*, method 2, rhombs, m. p. 98—99·5° (Found: C, 46·3; H, 4·9. $C_{12}H_{15}Cl_2NO_4$ requires C, 46·75; H, 4·9%). (16) N-*Methyl*-N-*phenyl*, method 3, needles m. p. 119·5—120° (Found: C, 58·3; H, 4·1. $C_{15}H_{13}Cl_2NO_2$ requires C, 58·1; H, 4·2%). (17) NN-*Diphenyl*, method 2, needles, m. p. 124·5—125° (Found: C, 64·5; H, 4·0. $C_{20}H_{15}Cl_2NO_2$ requires C, 64·5; H, 4·0%).

Rates of Hydrolysis of the Amides.—Procedure 1; *bases insufficiently strong to interfere in direct titration.* Approximately 0·01 mole of the amide was weighed into a flask, followed by 100 ml.

Rates of hydrolysis of 2,4-dichorophenoxyacetamides, determined in 0·22N-*potassium hydroxide in alcohol containing* 10% *v/v of water.*

Compd. No.	$Cl_2C_6H_3{\cdot}O{\cdot}CH_2{\cdot}CO{\cdot}NRR'$ R	R′	Temp. (° c)	10^3k (min.$^{-1}$)	$t_{\frac{1}{2}}$ (50°) (min.)
1	H	H	40	7·8 ± 0·83	90 ± 9·4 [b]
1	H	H	50	14 ± 1·9	50 ± 6·8
2	H	Me	50	2·1 ± 0·10	330 ± 14
3	H	Et	50	0·98 ± 0·085	710 ± 52
4	H	Pr^i	50	0·12 ± 0·0050	5800 ± 170
5	H	$CH_2{\cdot}CH_2{\cdot}OH$	50	3·1 ± 0·11	220 ± 7·9
6	H	Ph	50	2·7 ± 0·14	260 ± 10
7	H	C_6H_4Me-*p*	50	2·1 ± 0·14	330 ± 22
8	H	$C_6H_4{\cdot}NO_2$-*p*	50	— [a]	<20
9	H	$C_6H_4{\cdot}NO_2$-*m*	50	9·7 ± 0·69	72 ± 5·1
10	H	$C_6H_4{\cdot}NH_2$-*p*	50	2·8 ± 0·21	250 ± 19
11	H	$C_6H_4{\cdot}NH_2$-*m*	50	3·8 ± 0·42	185 ± 20
12	H	C_6H_4Cl-*p*	50	3·6 ± 0·12	190 ± 6·5
13	H	$C_6H_3Cl_2$-3,4	50	6·7 ± 0·65	100 ± 10
14	Me	Me	50	14 ± 1·5	50 ± 5·5
15	$CH_2{\cdot}CH_2{\cdot}OH$	$CH_2{\cdot}CH_2{\cdot}OH$	50	— [a]	<20
16	Me	Ph	50	5·2 ± 0·30	130 ± 7·7
17	Ph	Ph	40	~20	~30 [b]

[a] Reaction was too rapid to be followed by method employed. [b] $t_{\frac{1}{2}}$ values at 40°.

of alcohol containing 20% of water by volume. When the flask and the corresponding blank had reached the thermostatically controlled equilibrium temperature 100 ml. of 0·45N-alcoholic potassium hydroxide were added rapidly. Samples were taken immediately from each flask, the test sample being chilled rapidly to stop reaction. Aliquot portions of test and blank

[3] Synerholm and Zimmerman, *Contribn. Boyce Thomson Inst.*, 1947, **14**, 369.
[4] Newman, Fones, and Renoll, *J. Amer. Chem. Soc.*, 1947, **69**, 718.
[5] Maruyama and Moriwaki, *J. Agric. Chem. Soc. Japan*, 1952, **26**, 232.
[6] Clark and Hams, *Biochem. J.*, 1953, **55**, 839.

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solution were then titrated with standard 0·1N-hydrochloric acid, phenolphthalein being used as indicator. Sampling was repeated at intervals. The difference between the blank and test solution titres was taken as a measure of the amount of 2,4-dichlorophenoxyacetic acid produced by hydrolysis of the amide.

Procedure 2. *Bases too strong to permit direct titration.* When strong bases, *e.g.* ammonia, ethanolamine, were products of the hydrolysis, direct titration of the excess of potassium hydroxide was not possible. The blank flask was omitted. Samples were taken at intervals from the test flask, chilled rapidly, and aliquot portions pipetted directly into an excess of *ca.* 0·5N-hydrochloric acid. The liberated 2,4-dichlorophenoxyacetic acid was extracted several times with ether, the combined ether solutions were washed until free from aqueous mineral acid, and evaporated, and the residue dissolved in aqueous alcohol and titrated with standard alkali.

Comparative runs on the same compound by both methods gave good agreement. At least two runs, in most cases three, were carried out on each compound. Samples were taken at intervals of 30 or 60 min., depending upon the rate of reaction. In the case of the isopropylamide (4) which was hydrolysed very slowly, samples were taken at intervals of 8 and 16 hr. alternately. 6—8 samples were taken during the course of each run.

The first-order rate constants and half-life periods obtained are shown in the Table.

Discussion

Alkaline hydrolysis of amides is a bimolecular reaction [7,8] but under the conditions used, *i.e.*, a 5-molar excess of alkali, the kinetics of the reaction approximated very closely to first order. Plots of log[amide] against time did not deviate seriously from a straight line until at least 60% of the amide was hydrolysed. Since the principal aspect of the investigation, *i.e.*, relationship of chemical structure and stability to plant growth-regulating activity, was concerned only with the comparative stabilities of the compounds, this information was obtained in the form of half-life values calculated from the first-order rate constants.

Previous work on the alkaline hydrolysis rates of amides has been concerned with the effect of substituents in that portion of the molecule derived from the acid, and not, as in the present case, with varying substituents on the amide nitrogen. The mechanism of the reaction involves nucleophilic attack by a hydroxyl ion on the carbonyl carbon atom as the rate-determining step,[9] and the reaction will be accelerated by electron-withdrawing groups and retarded by electron-donating groups. The results now obtained show that this holds good for substituents on the amide nitrogen as well as those attached to the carbonyl carbon atom. The effect of donor groups is very noticeable in the case of methyl, ethyl, and isopropyl substituents. It could be argued that this effect is enhanced by steric retardation but when the very high hydrolysis rate of the disubstituted amides with bulky substituents, *e.g.* the diphenyl-amide, is taken into consideration this argument loses force. It appears, therefore, that the *N*-substituent is not sufficiently close to the site of reaction to have any marked steric effect.

There is no previous reference to comparison of hydrolysis rates of mono- and disubstituted amides, and it is noteworthy that the disubstituted amides are hydrolysed more rapidly than the corresponding monosubstituted amides. This is the case even though the substituents, taken individually, do not function as electron-withdrawing groups. No satisfactory explanation of this is offered.

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Research Department, African Explosives and Chemical Industries Limited,
P.O. Northrand, Transvaal. [*Received, October 27th*, 1960.]

[7] E. E. Reid, *Amer. Chem. J.*, 1899, **21**, 284, as quoted by Ingold.[9]
[8] Meloche and Laidler, *J. Amer. Chem. Soc.*, 1951, **73**, 1712.
[9] Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons, London, 1953, 784.

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454. *Aspects of Stereochemistry. Part VI.* Configuration of the 5-Hydroxy-2-p-nitrophenyl-1,3-dioxans and Further Observations on* trans*-5-Hydroxy-2-phenyl-1,3-dioxan.*

By B. Dobinson and A. B. Foster.

trans-5-Hydroxy-2-phenyl-1,3-dioxan (*trans*-1,3-*O*-benzylideneglycerol) is obtained by reduction of 5-oxo-2-phenyl-1,3-dioxan or of its hydrate. The alcohol yields only derivatives of *trans*-configuration on esterification and etherification, and a previous report to the contrary is corrected. Configurations have been assigned to the 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxans (1,3-*O*-*p*-nitrobenzylideneglycerols) and their benzoates and methyl ethers. The alcohols were hitherto unknown.

The 5-hydroxy-2-phenyl-1,3-dioxan of m. p. 63—64° was first described by Verkade and van Roon [1] and subsequently allocated the *trans*-configuration.[2] Mixtures of *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxan are easily obtained [2] by reaction of glycerol with benzaldehyde, and the pure *cis*-isomer is readily isolated by fractional crystallization. The *trans*-isomer cannot be isolated in this way, probably because of the tendency of the molecular complex of *cis*- and *trans*-isomers to crystallise. Melting points are singularly unreliable in assessing the purity of preparations of *trans*-5-hydroxy-2-phenyl-1,3-dioxan since those of the *trans*-isomer and the molecular complex are almost identical and little different from those of *cis*–*trans*-mixtures with 50% or less of *cis*-isomer. Chromatography of a mixture of *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxan on alumina [2] gave an apparent separation, but reinvestigation has shown that, whereas pure *cis*-isomer is eluted first, *cis*–*trans*-mixtures are subsequently released followed by a negligible amount of pure *trans*-isomer. The compound previously believed [2] to be *trans*-5-hydroxy-2-phenyl-1,3-dioxan has now been identified as a *cis*–*trans*-mixture. The extent of contamination of *trans*- by *cis*-isomer may be assessed conveniently by infrared spectroscopy on the basis of the strong absorptions at 808 and 832 cm.$^{-1}$ shown by *cis*- but not by *trans*-5-hydroxy-2-phenyl-1,3-dioxan.

trans-5-Hydroxy-2-phenyl-1,3-dioxan can also be obtained by reduction of 5-oxo-2-phenyl-1,3-dioxan [3] with lithium aluminium hydride or of its hydrate [3] with sodium borohydride; the *cis*-isomer apparently is not formed in these reactions. Reduction of related cyclohexanone derivatives [4] yields predominantly, but not exclusively, *trans*-alcohols.

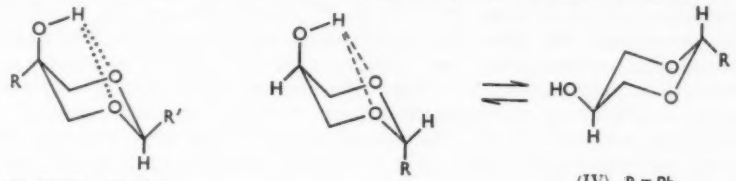
Intermolecular hydrogen bonding does not occur in solutions of the 2-hydroxy-5-phenyl-1,3-dioxans in carbon tetrachloride which are $<0{\cdot}005$M, so that the extent of intramolecular hydrogen bonding may be assessed,[5,6] approximately, from the extinction coefficients for free and bonded hydroxyl groups. *cis*-5-Hydroxy-2-phenyl-1,3-dioxan showed absorption for bonded hydroxyl groups only, at 3590 cm.$^{-1}$ (ε 95), indicating exclusive existence in conformation (I). The stereochemistry of this molecule and the nature of the hydrogen bond have been discussed elsewhere.[2] The marked tendency of 5-oxo-2-phenyl-1,3-dioxan to form a hydrate (II), which is not shown by 4-phenylcyclohexanone, may be due to stabilization by hydrogen bonding. The hydrate (II) is structurally closely related to *cis*-5-hydroxy-2-phenyl-1,3-dioxan (I) and one of its hydroxyl groups should be hydrogen-bonded. In dilute solution in carbon tetrachloride, 5,5-dihydroxy-2-phenyl-1,3-dioxan showed absorptions of similar intensity at 3540 and 3621 cm.$^{-1}$ for bonded and free hydroxyl groups respectively. The $\Delta\nu$ value [5,6] of 81 is

* Part V, *J.*, 1960, 2582.

[1] Verkade and van Roon, *Rec. Trav. chim.*, 1942, **61**, 831.
[2] Baggett, Brimacombe, Foster, Stacey, and Whiffen, *J.*, 1960, 2574.
[3] Marei and Raphael, *J.*, 1960, 886.
[4] Eliel and Ro, *J. Amer. Chem. Soc.*, 1957, **79**, 5992.
[5] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; 1954, **76**, 4323.
[6] Cole and Jefferies, *J.*, 1956, 4391.

much higher than that (41) of, for example, 5-hydroxy-1,3-dioxan [7] and is indicative [5] of a strong hydrogen bond.

Pure *trans*-5-hydroxy-2-phenyl-1,3-dioxan showed absorptions at 3633 (ε 79) and 3601 cm.$^{-1}$ (ε 26) for free and bonded hydroxyl groups, indicating an equilibrium mixture of the conformations (III) and (IV) with only a minor proportion of the molecules in conformation (III). The conformation (III) contains a phenyl group in the sterically unfavourable [8] axial position and the fact that a proportion of the molecules is in this



(I) R = H, R′ = Ph
(II) R = OH, R′ = Ph
(VII) R = H, R′ = *p*-$NO_2 \cdot C_6H_4$

(III) R = Ph
(V) R = *p*-$NO_2 \cdot C_6H_4$

(IV) R = Ph
(VI) R = *p*-$NO_2 \cdot C_6H_4$

conformation reflects the strength of the intramolecular hydrogen bond. Comparable effects have been noted in related compounds.[2] Both *trans*-2- and *trans*-5-deutero-5-hydroxy-2-phenyl-1,3-dioxan show absorptions in the hydroxyl stretching region [9] closely similar to those of the parent, undeuterated compound.

A comparison may be made between hydrogen-bonding effects in derivatives of cyclohexane-*trans*-1,2-diol and 5-hydroxy-1,3-dioxan. Intramolecular hydrogen bonding in these compounds involves the formation of five-membered rings, and, moreover, the similar $\Delta\nu$ values [5,7] indicate bonds of similar strength. 1-Isopropylcyclohexane-*trans*-1,2-diol exists exclusively, in dilute carbon tetrachloride solution, in the chair conformation with the isopropyl group equatorial and the hydroxyl groups axial.[6] The bulk of the isopropyl group is sufficient to anchor the molecule in one conformation and counteract any tendency of intramolecular hydrogen bonding to stabilise the alternative chair conformation with equatorial hydroxyl groups; the ethyl group is not so effective an anchor. The effective bulk of the phenyl group appears from models to be somewhat less than that of the isopropyl group and it is clear that it is not quite adequate to anchor *trans*-5-hydroxy-2-phenyl-1,3-dioxan in conformation (IV). The relative effect of the t-butyl group should be evident in *trans*-5-hydroxy-2-t-butyl-1,3-dioxan and the synthesis of this compound is being attempted.

Acetylation, benzoylation, and *p*-phenylazobenzoylation [10] of *trans*-5-hydroxy-2-phenyl-1,3-dioxan yielded chromatographically homogeneous esters of which that from the last reaction was new. All the esters afforded homogeneous *trans*-5-hydroxy-2-phenyl-1,3-dioxan on saponification. The compound, previously used in esterification studies [2] and believed to be *trans*-5-hydroxy-2-phenyl-1,3-dioxan is now known to have been a *cis–trans*-mixture. On chromatography of a mixture of *cis*- and *trans*-2-phenyl-5-*p*-phenylazobenzoyloxy-1,3-dioxan on alumina, the *trans*-ester was eluted first, paralleling the behaviour of the acetates and benzoates.[2]

Methylation of *trans*-5-hydroxy-2-phenyl-1,3-dioxan gave a homogeneous ether; this also has the *trans*-configuration as its affinity for alumina is less than that of the isomer obtained by methylation of the *cis*-alcohol. A parallel with the behaviour of the benzyl ethers [2] is provided and the configuration of all these ethers has been confirmed by nuclear magnetic resonance spectroscopy.[11]

[7] Barker, Brimacombe, Foster, Whiffen, and Zweifel, *Tetrahedron*, 1959, **7**, 10.
[8] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.
[9] Dobinson and Foster, unpublished results.
[10] Baggett, Foster, Haines, and Stacey, *J.*, 1960, 3528.
[11] Baggett, Dobinson, Foster, Homer, and Thomas, *Chem. and Ind.*, 1961, 106.

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Hibbert and Sturrock [12] considered the cyclic acetal, m. p. 88° rising to 99° on storage, obtained from the reaction of glycerol and *p*-nitrobenzaldehyde to be *cis–trans*-5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan (*cis–trans*-1,3-*O*-*p*-nitrobenzylideneglycerol). The ring size was shown [13] by the fact that the two methyl ethers obtained from the *cis–trans*-alcohol mixture could also be obtained by condensation of 2-*O*-methylglycerol with *p*-nitrobenzaldehyde.[13,14] Although two benzoates were obtained [13] from the *cis–trans*-alcohol mixture their saponification was not recorded. Repetition of this work gave *cis–trans*-5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan with m. p. 88° which rose rapidly to 95—98° on storage; it seems likely that these two modifications are dimorphs.[15] Benzoylation of the *cis–trans*-alcohol mixture gave [13] two esters, m. p. 159° and 206° to which the *cis*- and *trans*-configurations, respectively, have been allocated on the following evidence. On chromatography on alumina, the benzoate of m. p. 206° had the weaker affinity for the adsorbent and the *trans*-configuration may be allocated tentatively on analogy with the behaviour of the 5-benzoyloxy-2-phenyl-1,3-dioxans. Saponification of the benzoate (m. p. 206°) gave a 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan, m. p. 134—135°, which can be allocated the *trans*-configuration since, in 0·005M-carbon tetrachloride solution, it has $\nu_{max.}$ for free and bonded hydroxyl groups at 3632 (ε 110) and 3602 cm.$^{-1}$ (ε 30). This absorption pattern, which is closely similar to that noted above for *trans*-5-hydroxy-2-phenyl-1,3-dioxan, indicates the existence of an equilibrium mixture of the conformations (V) and (VI) in which the latter predominates. Saponification of the benzoate of m. p. 159° gave a 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan, m. p. 108—109°, which had $\nu_{max.}$ for bonded hydroxyl at 3593 cm.$^{-1}$ (ε 90) and a very weak absorption at 3633 cm.$^{-1}$ for free hydroxyl groups indicative of *cis*-configuration and predominant existence in conformation (V). This result closely parallels that noted above for *cis*-5-hydroxy-2-phenyl-1,3-dioxan. *cis–trans*-5-Hydroxy-2-*p*-nitrophenyl-1,3-dioxan had $\nu_{max.}$ for free and bonded hydroxyl groups at 3631 (ε 65) and 3594 cm.$^{-1}$ (ε 71), showing it to be an approximately equimolar mixture.

Attempts to resolve *cis–trans*-5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan completely by chromatography on alumina were unsuccessful. A small proportion of the *trans*-alcohol was eluted first followed by *cis–trans*-mixture; the *trans*-alcohol, surprisingly, has the weaker affinity for alumina. The chromatographic properties of the 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxans may be affected, if not dominated, by the nitro-group since a significantly more polar solvent mixture was required to elute the 5-hydroxy-2-*p*-nitrophenyl-1,3-dioxans than the 5-hydroxy-2-phenyl-1,3-dioxans from alumina.

cis–trans-5-Hydroxy-2-*p*-nitrophenyl-1,3-dioxan was readily converted into a mixture of methyl ethers [13] which could be separated by chromatography on alumina to yield pure isomers with m. p. 139° and 106°. By analogy with the behaviour of the benzyl and methyl ethers of 5-hydroxy-2-phenyl-1,3-dioxan the isomer of m. p. 139°, which had the greater affinity for alumina, may be tentatively assigned the *cis*-configuration. Equilibration of each of the methyl ethers at room temperature in benzene containing hydrogen chloride gave a mixture containing *ca.* 70% of the isomer, m. p. 106°, to which the *trans*-configuration may therefore be allocated on the basis of arguments detailed in a previous paper.[2]. The assigned configurations have been confirmed by nuclear magnetic resonance spectroscopy.[11]

Experimental

Light petroleum refers to the fraction of b. p. 60—80°.

trans-5-*Hydroxy*-2-*phenyl*-1,3-*dioxan*.—(*a*) A solution of 2-phenyl-1,3-dioxan-5-one [3] (1 g.) in ether (*ca.* 20 ml.) was added to a slurry of lithium aluminium hydride (0·5 g.) in ether (50 ml.),

[12] Hibbert and Sturrock, *J. Amer. Chem. Soc.*, 1928, **50**, 3374.
[13] Hibbert and Carter, *J. Amer. Chem. Soc.*, 1928, **50**, 3376.
[14] Hibbert, Whelen, and Carter, *J. Amer. Chem. Soc.*, 1929, **51**, 302.
[15] Dobinson, Foster, and Stacey, *Tetrahedron Letters*, 1959, No. 1, p. 1.

and the mixture was boiled under reflux for 2 hr. Excess of reducing agent in the cooled mixture was decomposed with ethyl acetate. After addition of water the mixture was filtered and the residue was washed with ether. Evaporation of the combined and dried (Na_2CO_3) ethereal solutions gave a solid residue which recrystallised from benzene–light petroleum, yielding *trans*-5-hydroxy-2-phenyl-1,3-dioxan (0·55 g., 54%), m. p. 63—64°.

(*b*) A solution of 5,5-dihydroxy-2-phenyl-1,3-dioxan [9] (0·1 g.) and sodium borohydride (0·2 g.) in ethanol (30 ml.) was stored at room temperature for 1 day. The pH of the mixture was adjusted to 7 with acetic acid and the solution was then evaporated to dryness in the presence of sodium carbonate. The residue was extracted with benzene, the extract was concentrated, and the residue recrystallised from benzene–light petroleum to yield *trans*-5-hydroxy-2-phenyl-1,3-dioxan (35 mg., 38%), m. p. 63—64°.

In neither product was the *cis*-isomer detected.

Infrared Spectra of the 5-Hydroxy-2-phenyl-1,3-dioxans.—The extent of contamination of samples of *trans*-5-hydroxy-2-phenyl-1,3-dioxan with the *cis*-isomer can be assessed from the infrared spectra (Nujol mull or KCl disc) since the *cis*-compound has absorptions (cm.$^{-1}$) at 808s, 832s, 931s, 1083w, 1290b, and 1342b which are not present in the spectrum of the *trans*-isomer. However, only the absorptions at 808 and 832 cm.$^{-1}$ may be used reliably to detect the *cis*-isomer. The spectrum of an equimolar *cis–trans*-mixture showed a broad absorption at 1087 cm.$^{-1}$ but not the absorptions at 931, 1083, 1290, and 1342 cm.$^{-1}$. Mixtures containing more than 50% of the *trans*-compound absorbed at 931 cm.$^{-1}$.

The spectra in the hydroxyl stretching region were obtained from CCl_4 solutions of the alcohols in 2 or 3 cm. layers (fused quartz cells), by means of a Unicam S.P. 100 spectrometer equipped with a grating (3000 lines per in.). Frequencies were checked against water vapour and ammonia bands. The concentration of the alcohols was always $<0{\cdot}005$M in order to eliminate intermolecular hydrogen bonding; the extinction coefficients, ε, are maximum values and are equal to $(1/cl)\log_{10}(I_0/I)$ with l in cm. and c in moles/l. *cis*-1,3-*O*-Benzylideneglycerol had $\nu_{max.}$ at 3590 cm.$^{-1}$ (ε 95) for bonded hydroxyl groups and the *trans*-isomer at 3633 (ε 79) and 3601 cm.$^{-1}$ (ε 26) for free and bonded hydroxyl groups respectively.

Chromatographic Behaviour of the 5-Hydroxy-2-phenyl-1,3-dioxans.—A solution of the 5-hydroxy-2-phenyl-1,3-dioxan(s) (*ca.* 90 mg.) in benzene (3 ml.) was introduced on to alumina [2] (10 g.; activity Brockmann III), and the column was eluted with benzene. Fractions (20 ml.) were collected and their contents (mg.) are shown in the Table. The fractions obtained from the *cis–trans*-mixture were analysed qualitatively by infrared spectroscopy; fractions 5 and 6 contained *cis*-isomer, fractions 7—15 *cis–trans*-mixtures with progressively less *cis*-isomer, and fraction 16 *trans*-isomer.

Behaviour of the 5-hydroxy-2-phenyl-1,3-dioxans on alumina.

Fraction	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Recovery (%)
cis-Isomer ...	8·0	16·8	11·0	9·7	7·6	5·7	5·2	4·6	4·0	2·5	2·0	7·9[a]					96·0
trans-Isomer				7·1	11·4	8·9	8·0	7·4	6·7	6·0	5·6	4·8	4·0	3·5	2·3	9·2[a]	94·5
1 : 1 *cis–trans*-Mixture			6·2	17·8	11·5	9·3	15·0	12·0	7·6	5·2	4·4	3·8	2·3	8·5[a]			97·6

[a] Residual material on the column eluted with ether.

Derivatives of trans-5-*Hydroxy-2-phenyl-1,3-dioxan.*—Treatment of *trans*-5-hydroxy-2-phenyl-1,3-dioxan (40 mg.) with *p*-phenylazobenzoyl chloride (82 mg., 1·5 mol.) in dry pyridine (3 ml.) by the method previously described [10] gave a chromatographically homogeneous p-*phenylazobenzoate* (78 mg., 89%), m. p. 190—191° (from benzene–light petroleum) (Found: C, 70·9; H, 5·4; N, 7·4. $C_{23}H_{20}N_2O_4$ requires C, 71·1; H, 5·2; N, 7·2%). Saponification of the *p*-phenylazobenzoate regenerated chromatographically homogeneous *trans*-5-hydroxy-2-phenyl-1,3-dioxan.

Methylation of *trans*-5-hydroxy-2-phenyl-1,3-dioxan (0·25 g.) with ether (2·5 ml.), methyl iodide (25 ml.), and silver oxide (0·25 g.) in the usual manner gave the *methyl ether* (110 mg., 44%), b. p. 121—123°/0·1 mm., m. p. 40—42° (without recrystallization) (Found: C, 67·7; H, 7·1. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%).

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5-Hydroxy-2-p-nitrophenyl-1,3-dioxans.—(a) cis–trans-*Mixture*. *cis–trans*-5-Hydroxy-2-*p*-nitrophenyl-1,3-dioxan (37%) was prepared by essentially the method of Hibbert and Carter [13] and had m. p. 88—90° which rose rapidly to 96—98° on storage. Hibbert and Carter [13] record a similar behaviour. Melting and resolidification of the compound m. p. 88—90° gave the compound m. p. 96—98°. It is likely that these compounds are dimorphs.

(b) cis- *and* trans-*Isomers*. *cis–trans*-5-Benzoyloxy-2-*p*-nitrophenyl-1,3-dioxan (62 mg.), prepared by essentially the method of Hibbert and Carter,[13] was fractionated on alumina (5 g.) by elution with benzene–light petroleum (2 : 3), yielding, first, the *trans*-isomer (27 mg.), m. p. 206° (from benzene–light petroleum), and then the *cis*-isomer (30·5 mg.), m. p. 159° (from benzene–light petroleum). The *cis–trans*-mixture (3 g.) was dissolved in the minimum volume of ethyl acetate at 70° and the solution cooled slowly. The separated product after recrystallization was *trans*-5-benzoyloxy-2-*p*-nitrophenyl-1,3-dioxan (0·6 g.), m. p. 206°. The mother liquors at 0° yielded more of the *trans*-compound. The remaining solution was concentrated to one-third volume and cooled to −15°. The separated product was combined with that obtained by repetition of the process and recrystallized from benzene–light petroleum (b. p. 60—80°), yielding *cis*-5-benzoyloxy-2-*p*-nitrophenyl-1,3-dioxan (0·7 g.), m. p. 159°.

The benzoates were saponified as follows. A solution of the benzoate (124 mg.) in chloroform (3 ml.) was treated with sodium methoxide obtained from sodium (1·1 mol.) and methanol (5 ml.). The mixture was heated to the b. p., then cooled, the excess of alkali was neutralised with carbon dioxide, and the solution evaporated. The residue was extracted with benzene, washed with water, dried ($MgSO_4$), and recovered. The products appeared to be homogeneous by chromatography on alumina. Thus, cis-5-*hydroxy*-2-p-*nitrophenyl*-1,3-*dioxan*, m. p. 108—109° (from benzene–light petroleum), was obtained from the benzoate of m. p. 159° (Found: C, 53·3; H, 5·2; N, 6·0. $C_{10}H_{11}NO_5$ requires C, 53·3; H, 4·9; N, 6·2%), and likewise the benzoate, m. p. 209°, gave trans-5-*hydroxy*-2-p-*nitrophenyl*-1,3-*dioxan*, m. p. 134—135° (from benzene–light petroleum) (Found: C, 53·3; H, 4·9; N, 6·3%).

Solutions (0·005M) of the alcohols in CCl_4 showed the following $\nu_{max.}$ for free and bonded hydroxyl groups: *trans*-isomer 3632 (ε 110) and 3602 cm.$^{-1}$ (ε 30); *cis*-isomer 3633 (very weak) and 3593 cm.$^{-1}$ (ε 90).

5-Methoxy-2-p-nitrophenyl-1,3-dioxans.—The mixture (125 mg.) of methyl ethers obtained by methylation [13] of *cis–trans*-5-hydroxy-2-*p*-nitrophenyl-1,3-dioxan (m. p. 98—100°) was readily fractionated on alumina (10 g.) by elution with benzene–light petroleum (1 : 3) followed by ether–benzene–light petroleum (1 : 5 : 14), to yield *trans*-5-methoxy-2-*p*-nitrophenyl-1,3-dioxan (44 mg.), m. p. 106—107° (from benzene–light petroleum), and *cis*-isomer (41 mg.), m. p. 138—139° (from benzene–light petroleum). The mixture was also separated by fractional crystallization as described by Hibbert and Carter.[13]

Separate solutions of the *cis*- and *trans*-methyl ethers (100·8 mg.) in benzene (5 ml.) and in benzene (4 ml.) which had been saturated with dry hydrogen chloride were stored at room temperature for 4 weeks. The solutions were then neutralised with sodium carbonate and evaporated and the residues fractionated by chromatography on alumina. The *cis*-methyl ether yielded a mixture containing 69% of *trans*- and 31% of *cis*-isomer, and the *trans*-methyl ether gave a mixture containing 68% of *trans*- and 32% of *cis*-isomer.

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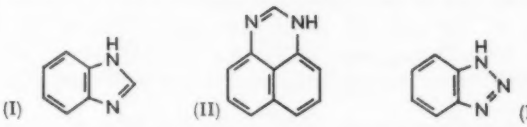
455. *The Infrared Spectra of Some Simple Benzimidazoles.*

By K. J. Morgan.

Infrared spectra of some simple alkyl-, perfluoroalkyl-, and carboxyl-substituted benzimidazoles and of some of their simple derivatives and analogues are reported and discussed.

While the infrared spectrum of imidazole [1] and of some of its simple derivatives and salts [2] have been discussed, the spectra of few benzimidazoles have been recorded in the literature.[3] As the benzimidazole ring system (I) is of considerable chemical and biological interest it seemed desirable that fuller information of its spectroscopic characteristics should be available. The preparation (for other purposes) of a number of benzimidazoles has enabled us to investigate their spectra; the results are reported in this paper.

The spectra of solid specimens of the simple alkyl- and perfluoroalkyl-benzimidazoles are characterised by a series of strong, broad bands in the region 2400—3200 cm.$^{-1}$; they show no band in the region normally associated with the simple N–H stretching frequency (Fig. 1). In solution (concentration $<0{\cdot}01$ mole/l.) this region of the spectrum is completely changed: the broad-banded absorption is replaced by a single sharp band near 3400 cm.$^{-1}$ which must be ascribed to the N–H stretching vibration. It has been shown that in relatively concentrated solutions (0·02—0·6 mole/l.) benzimidazoles are strongly associated [4] and indeed the spectra of more concentrated solutions (0·01—0·03 mole/l.) possess a broad band near 3200 cm.$^{-1}$ indicating the presence of polymeric association.



It seems beyond doubt that the strong bands near 2400—3200 cm. in the spectra of the solid benzimidazoles are best ascribed to a strong hydrogen bond of the type N–H···N showing proton transfer.[5] This receives confirmation from examination of the spectra of a number of 1-deuterated benzimidazoles. The strong, banded absorption is displaced to a *ca.* 2200 cm.$^{-1}$ and it is simultaneously rendered less diffuse (Fig. 1). Equally significantly,[6] the ratio ν(N–H) : ν(N–D) [the value of ν(N–H) being taken for the centre of the strong bands] is approximately 1·30. Together, these facts indicate that the association is weaker for the deuterated compounds and in accordance with the representation of the hydrogen bond as a proton-transfer system.

The position of the N–H bands in the spectra of solutions of benzimidazoles (Table 1) is similar to that found for pyrroles [7] and indoles; [8] the bands show typical displacements (of +10—20 cm.$^{-1}$) when tetrachloroethylene replaces methylene chloride as solvent. The effect of substituents is in accord with expectation: the small increases in frequency of the alkyl derivatives and the larger decreases in frequency of the perfluoroalkyl compounds diminish as the orientation of substitution varies: 2- > 4- ⩾ 5-. It seems probable that these shifts are due mainly to induction and that there is little hydrogen bonding to adjacent fluorine atoms (this would have necessitated a larger shift for 4-perfluoroalkyl compounds), but re-examination of these bands under conditions of greater

[1] Garfinkel and Edsall, *J. Amer. Chem. Soc.*, 1958, **80**, 3807.
[2] Otting, *Chem. Ber.*, 1956, **89**, 1940, 2887.
[3] Randall, Fowler, Fuson, and Dangl, "Infrared Determination of Organic Structures," Van Nostrand, New York, 1949, p. 216; Baganz and Pflug, *Chem. Ber.*, 1956, **89**, 691; O'Sullivan, *J.*, 1960, 3278.
[4] Hunter and Marriot, *J.*, 1941, 777.
[5] Cannon, *Spectrochim. Acta*, 1958, **10**, 341.
[6] Bellamy and Rogasch, *Proc. Roy. Soc.*, 1960, *A*, **257**, 98.
[7] Eisner and Erskine, *J.*, 1958, 971.
[8] Millich and Becker, *J. Org. Chem.*, 1958, **23**, 1096.

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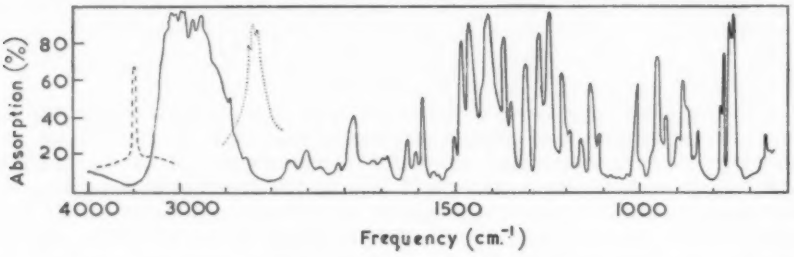
dispersion would be of interest. The intensities of the N–H bands show analogous variations. In general, those compounds with perfluoroalkyl substituents show more intense absorption, giving both higher values of extinction coefficients and broader bands, but no simple correlation between orientation of substitution and intensity is apparent.

Bands derived primarily from aromatic C–C and C–N stretching modes are found in the region 1620—1500 cm.$^{-1}$. In the spectrum of benzimidazole itself (Fig. 1) and of

FIG. 1. *Infrared spectrum of benzimidazole.* —— *Mull with Nujol or Fluorolub;* — — — *solution in methylene chloride;* . . . . *1-deuterobenzimidazole, mull with Nujol or Fluorolub.*



those derivatives which carry no substituent in the heterocyclic ring a consistent pattern of three weak bands is found in this region, near 1620, 1600, and 1500 cm.$^{-1}$ (Tables 1, 2). When the heterocyclic ring is substituted, a fourth band of variable intensity appears near 1550 cm. (Fig. 2; Tables 1, 2). (The band near 1500 cm.$^{-1}$ is frequently partly masked in solution by a strong band in the spectrum of the solvent.) Other bands probably derived from C–C stretching modes appear near 1420 and 1460 cm.$^{-1}$.

TABLE 1. *Some characteristic bands in the spectra of solutions*[a] *of benzimidazoles and some related compounds.*

	N–H bands			Other bands							
Benzimidazole	ν[b]	ε[c]	f[d]	ν	ε	ν	ε	ν	ε	ν	ε
Unsubst.	3460	130	4·5	1620	25	1603, 1592	40	—	—		
2-Me	3460	125	4·9	1622	30	1599	—	1542	105		
2-Et	3470	135	6·0	1620	35	1599	—	1540	160		
2-Pr^n	3460	120	5·4	1622	30	1591	—	1535	115		
2-Pr^i	3470	135	6·0	1622	25	1594	—	—	—		
4-Me	3460	135	5·3	1616	20	1599	15	—	—		
5-Me	3460	95	3·3	1618	—	1596	—	1543	80		
2,5-Me_2	3460	130	5·0	1620	40	1601	15	1548	95		
2-CF_3	3430	150	8·2	1625	10	1597	50	1538	40		
2-C_2F_5	3420	165	9·9	1618	—	1593	25	1538	45		
2-C_3F_7	3430	170	10·1	1618	10	1591	20	—	—		
4-CF_3	3430	140	7·1	1625	20	1610	10	—	—		
5-CF_3	3440	—	—	1632	—	1598	—	—	—		
2-Me-4-CF_3	3450	145	7·3	1627	50	1610	35	1545	105		
4-Me-2-CF_3	3440	200	10·9	1619	25	1601	40	1545	105		
4-Me-2-C_3H_7	3440	165	10·0	1620	20	1604	20	1532	50		
2,4-$(CF_3)_2$	3430	150	11·4	1628	—	1610	50	1554	85		
2,5-$(CF_3)_2$	3420	150	9·0	1632	—	—	—	1550	70		
2-Me-4,5-$(CF_3)_2$	3450	175	7·9	1642	35	1599	10	1545	115		
2,4,5-$(CF_3)_3$	3400	145	10·1	1626	—	—	—	1553	40		
5-MeO-2-CF_3	3440	165	9·0	1630	125	1619	90	1574	200		
4,5,6,7-F_4-2-CF_3	3390	85	5·2	—	—	1604	80	1566	410	1548	295
Other compounds											
Benzotriazole	3450	150	7·6	1618	30	1596	15	—	—	1510	10
Perimidine	3420	105	3·6	1632	185	1615	220	1596	200	—	—
2-Methylperimidine	3430	135	5·1	1635	250	1620	745	1595	405	1524	55
2-Ethylperimidine	3420	135	5·4	1635	260	1614	600	1596	410	1525	55
2-Propylperimidine	3420	130	5·2	1633	305	1615	685	1597	405	1524	55

[a] In methylene chloride. [b] Band frequency (in cm.$^{-1}$). [c] Extinction coefficient $= (1/cl)(\log T_0/T)$.
[d] $f = 10^{-8}\varepsilon \cdot \Delta\nu_{\frac{1}{2}}$.

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Bands which appear regularly in the spectra of the simple benzimidazoles near 1000 and 960 cm.$^{-1}$ may be associated with benzenoid ring breathing modes and bands near 760 and 880 cm.$^{-1}$ with heterocyclic ring breathing modes. Elsewhere the spectra of the alkyl-substituted compounds show absorption corresponding to the pattern of substitution.[9] Compounds containing trifluoromethyl groups show additional strong bands characteristic of aromatic trifluoromethyl compounds[10] (Table 2). The symmetrical C–F stretching

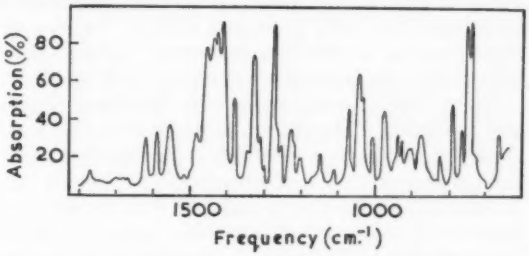

FIG. 2. *Infrared spectrum of 2-ethylbenzimidazole (mull with Nujol or Fluorolub).*

TABLE 2. *Some characteristic bands* (cm.$^{-1}$) *in the spectra*[a] *of alkyl- and perfluoroalkylbenzimidazoles.*

Benzimidazoles						[b]	[b]	[b]	[b]
Unsubst.	1621w	1605w 1591m	—	1500w	1351w	—	—	—	—
2-Me	1628m	1592w	1562m	1512w	—	—	—	—	—
2-Et	1626m	1595m	1547m	1510m	1330m	—	—	—	—
2-Pr^n	1625w	1592w	1540m	1508w	1320w	—	—	—	—
2-Pr^i	1620w	1590w	1540m	—	1324m	—	—	—	—
4-Me	1613w	1595mw	—	—	—	—	—	—	—
5-Me	1628w	1590w	—	—	1345w	—	—	—	—
2,4-Me$_2$	1622m	1604w	1553ms	1505w	—	—	—	—	—
2-CF_3	1625w	1597mw	1555m	1501mw	1329ms	1192s	1172s	1143ms 1132ms	—
2-C_2F_5	1625w	1596mw	1538mw	1500m	1345ms	—	1154s	—	—
2-C_3F_7	—	1595w	1536w	1499mw	1346s	—	1179ms	—	—
4-CF_3	1634mw	1611w	1540w	1492m	1338s	1188s	1178s	1122s	1110s
5-CF_3	1633mw	1604w	—	1510w	1335s	—	1175s	1125m	1100s
2-Me-4-CF_3	1624w	1608mw	1550m	1510m	1340ms	1195s	1165s	1127s	1119s
2-Me-5-CF_3	1634mw	1607w	1540m	—	1337s	—	1170s	1130s	1110s
4-Me-2-CF_3	1625mw	1610mw	1551m	1514mw	1325s	1182s	1170s	1142s	—
4-Me-2-C_3F_7	1625w	1610w	1540mw	1515mw	1325ms 1353s	1195s	1153s	1150s	1126s
5-Me-2-CF_3	1627mw	1612mw	1552ms	1515m	1325s	1188s	1175s	1144s	—
2,4-$(CF_3)_2$	1636w	1615w	1562w	1526m	1330s	—	1168s	1137s	—
2,5-$(CF_3)_2$	1630mw	1604w	1560m	1510mw	1329ms	1199s	1166s	1136s	1120s
4,5-$(CF_3)_2$	1645mw	1600w	—	1510w	1336s	1190s	—	1150s	—
5,6-$(CF_3)_2$	1660m	1610m	—	1525mw	1350s	1193s	1170s	1144s	1120s
2-Me-4,5-$(CF_3)_2$	1630mw	1601w	1555m	1492w	1333s	—	1176s	1148s	1135s
4,5-Me$_2$-2-CF_3	1632mw	1610mw	1545ms	1513w	1328s	1188s	1170s	1146s	—
5,6-Me$_2$-2-CF_3	—	1596w	1555ms	—	1332ms	1191s	1172s	1138s	1107s
2,4,5-$(CF_3)_3$	1653w	1606w	1570m	1500w	1345s	1190s	1162s	1148s	—
2-HO·CH_2	1622w	1594w	1547w	1533w	1349m	—	—	—	—
4-CF_3-2-CH_2·OH	1635m	1610m	1538m	1505w	1334s	1198s	1170s	—	1122s
5-CF_3-2-CH_2·OH	1635m	—	1545m	1502w	1332s	—	1168s	—	1125s
2-CH_2·CN	1622mw	1605w 1593w	1547m	1490mw	1325m	—	—	—	—
5-MeO-2-CF_3	1642m	1593w	1550ms	1504w	1344m	1175s	1163s	1130s	1118s
5-Cl-2-CF_3	—	1605mw	1558m	1500w	1325s	1195s	1170s	—	—
5-NO_2	1625w	1590mw	1560w	1518s 1491mw	1344s 1320s	—	—	—	—
5-NO_2-2-CF_3	1648w 1638w	1598w	1558m	1533s 1492s	1348s 1322s	1192s	1163s	—	—

[a] As mulls with Nujol and Fluorolub. [b] Only strong bands in this region are listed.

[9] Randle and Whiffen, "Molecular Spectroscopy," Institute of Petroleum, London, 1954.
[10] Randle and Whiffen, *J.*, 1955, 1311.

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band occurs close to 1330 cm.$^{-1}$ in both solid and solution spectra. The antisymmetrical CF_3 stretching frequency gives rise to two bands between 1100 and 1200 cm.$^{-1}$, but coupling of these vibrations with the out-of-plane C–H deformation modes produces several strong bands of mixed character. The spectra usually contain four strong bands in this region: *viz.*, near 1190, 1170, 1140, and 1120 cm.$^{-1}$; as a tentative correlation it was noted that those compounds with 2-trifluoromethyl groups absorb regularly at 1140 cm.$^{-1}$, and those with 4- or 5-trifluoromethyl groups at 1120 cm.$^{-1}$.

A number of compounds with structures closely related to the benzimidazoles were also examined. The spectra of perimidines (II) and benzotriazole (III) (Table 1) conform closely to the pattern established for benzimidazoles. Spectra of the solids show broad-banded absorption from 2400 to 3200 cm.$^{-1}$ which on deuteration is displaced to 2200 cm.$^{-1}$. In solution spectra these bonded N–H bands are replaced by sharp bands near 3400 cm.$^{-1}$. Bands near 1600 cm.$^{-1}$ also follow a pattern similar to that of the bands in the spectra of benzimidazoles. Perimidines show three strong bands, at 1595, 1615, and 1635 cm.$^{-1}$; an additional band at 1540 cm.$^{-1}$ (1520 cm.$^{-1}$ in solution) is shown by 2-alkyl-substituted compounds.

TABLE 3. *Bands (cm.$^{-1}$) in the spectra of some benzimidazolecarboxylic acids.*[a]

Acid	N–H and O–H		C=O	Other bands	
2-Benzimidazolylacetic	3400m 3160m	2200—2800w	1645s	1612s	1565m
2-Benzimidazolyldifluoroacetic	3380mw	2400—3100m	1690s	1625m	1535w
β-2-Benzimidazolylpropionic	—	2200—3200m	—	1635m 1600m	1550ms
β-2-Benzimidazolyltetrafluoropropionic	3400mw	2200—3000mw	1676s	1630mw	1540w
Benzimidazole-5-carboxylic	3200m	2200—2600w	1670s	1625m	—
Benzimidazole-5,6-dicarboxylic (monohydrate)	3400w 3140m	2300—3200m	1686s	[1620]	—
Benzimidazole-4-carboxylic	3400m 3200m	2200—2800m	1670w	1625s 1600s	1540m
2-Trifluoromethylbenzimidazole-4-carboxylic	3430m	2400—3200w	1700s	1630w 1607w	1543m
Benzimidazole-2-carboxylic	—	2200—3200s	1650s	[1620]	1520m
4-Trifluoromethylbenzimidazole-2-carboxylic	3500m	2200—3100ms	[1660]	1623s	—
5-Trifluoromethylbenzimidazole-2-carboxylic	—	2300—3200ms	1648s	—	1520m

[a] As mulls in Nujol and Fluorolub. [ ] denotes inflexion.

The spectra of the carboxylic acids derived from benzimidazole present some unexpected features. Hunter and Marriot [4] noted that when a carbonyl group is so located as to permit chelation with the benzimidazole N–H grouping, the compound is no longer strongly associated. 2-Benzimidazolyl-acetic acid and -difluoroacetic acid have spectra (Table 3) indicating a strongly bonded carbonyl group and discrete (though bonded) OH and NH groups: these compounds are undoubtedly correctly represented as the chelate compounds (IV) although some non-bonded material may be present in the fluoro-acid. β-2-Benzimidazolylpropionic acid shows marked differences. The carbonyl band is replaced by a broad band at 1550 cm.$^{-1}$ and the C–O stretching frequency is displaced to 1410 cm.$^{-1}$. These shifts and the absence of a discrete hydroxyl band indicate that this acid is best regarded as a zwitterionic compound (V). The high melting point (225°) of this acid may be compared with that of the acetic acid (123°). Conversely, the spectrum of β-2-benzimidazolyltetrafluoropropionic acid is closely similar to that of the difluoroacetic acid: it seems probable that the inductive effect of the adjacent fluorine grouping so reduces the basicity of the ring that salt formation is destabilized relative to the cyclic, hydrogen-bonded system. The formation of a 7-membered hydrogen-bonded ring is of interest; Hunter and Marriott [4] found no indication of chelation in solution when this would have led to a 7-membered ring.

Benzimidazole-2-carboxylic acid has a bonded carbonyl group but shows no discrete

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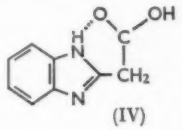
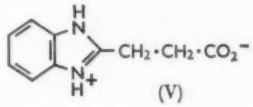
hydroxyl or amino-bands and is consequently best described by the unsymmetrical structure (VI) which is one of two equivalent tautomers. 5-Trifluoromethylbenzimidazole-2-carboxylic acid has a similar structure, but a band at 3500 cm.$^{-1}$ and a low carbonyl frequency suggest that the 4-trifluoromethyl analogue is best written as the


(IV)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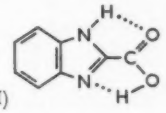
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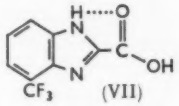
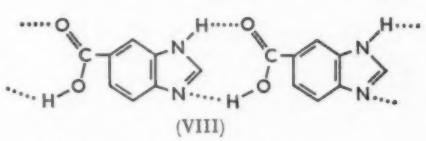
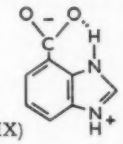
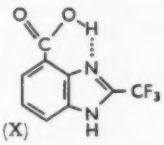

(VII)


(VIII)


(IX)


(X)

monobonded compound (VII). Proximity of the trifluoromethyl group to the heterocyclic ring will reduce the basic strength the ring (and increase the acidity of the N–H grouping) [11] and so stabilise the N–H···O bond at the expense of the O–H···N bond.

Benzimidazole-5-carboxylic and -5,6-dicarboxylic acid cannot show intramolecular bonding to the heterocyclic ring. The latter (as monohydrate) appears to be a simple carboxylic acid; the former shows a band at 3200 cm.$^{-1}$ which may well be derived from polymeric association of the carboxyl group with the heterocyclic ring (VIII). The spectrum of benzimidazole-4-carboxylic acid differs considerably from this and appears to be consistent with a hydrogen-bonded zwitterionic structure (IX); introduction of a 2-trifluoromethyl group profoundly modifies the spectrum. The carbonyl group is now largely non-bonded and the structure must be written with a bonded hydroxyl group and a free imino-group (X). Comparison of this structure with that of the unsubstituted acid shows that the presence of a 2-trifluoromethyl group reduces the basicity of the ring, so that the adjacent oxygen atom becomes a stronger basic centre than the ring nitrogen atom.

The acids proved insufficiently soluble in the usual solvents to permit the measurement of solution spectra.

Experimental.—Benzimidazoles were prepared and purified by conventional routes. Some of the fluorine-containing compounds have been described; [11,12] details of the properties of the others will be published elsewhere. 1-Deutero-, 1-deutero-2-ethyl-, and 1-deutero-2-trifluoromethyl-benzimidazole, 1-deutero-2-ethylperimidine, and 1-deuterobenzotriazole were prepared by crystallisation of the protium compound twice from deuterium oxide.

Spectra of the solids were determined for mulls with Nujol and Fluorolub; a few specimens were also examined as discs with potassium bromide: no significant differences could be detected. Spectra of solutions in methylene chloride were determined in matched cells; a few samples were also examined in tetrachloroethylene but the majority of the compounds were insufficiently soluble in this medium to yield useful spectra. Spectra were measured with a Perkin–Elmer model 21 spectrophotometer with sodium chloride optics.

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Department of Chemistry, The University,
Edgbaston, Birmingham, 15. [*Received, November 18th,* 1960.]

[11] Belcher, Sykes, and Tatlow, *J.*, 1954, 4159; Lane, *J.*, 1955, 534.
[12] Sykes and Tatlow, *J.*, 1952, 4078; Smith and Steinle, *J. Amer. Chem. Soc.*, 1953, **75**, 1292; Fernandez-Bolaños, Overend, Sykes, Tatlow, and Wiseman, *J.*, 1960, 4003.

456. *The Condensed Phases of Sulphur Trioxide. Part I. Vapour Pressure and Viscosity of the Liquid Phase at Low Temperatures.*

By R. A. Hyne and P. F. Tiley.

The vapour pressure and the viscosity of liquid sulphur trioxide have been measured in the range 17—50° c, and results previously reported have been critically reviewed. The following interpolation equations have been derived:

$$\log_{10} p \text{ (mm.)} = 7{\cdot}8663 - 1158{\cdot}9/(t + 188{\cdot}00) \text{ and}$$

$$\log_{10} \eta \text{ (cp.)} = -1{\cdot}3726 - (404{\cdot}82)\ T^{-1} + (2{\cdot}6583)10^5 T^{-2}$$

where t is expressed in °c and T in °k. Calculated values of the molar latent heat of evaporation show a continuous decrease from 10·5 kcal. at 20° to 9·6 kcal. at 50°. The variations of latent heat and of vapour pressure with temperature are discussed for the case of associated liquids, and the behaviour of sulphur trioxide is compared with that of dinitrogen tetroxide and of acetic acid.

Industrial demand for liquid sulphur trioxide has focused attention on the complex nature of the condensed phases of this compound, and on the uncertainties about some of the values of its basic physical properties.[1]

There are at least three solid phases: γ-SO_3 consists mainly of cyclic trimer with possibly some monomer present; β-SO_3 consists of polymeric molecules arranged in helical chains of unknown length; and α-SO_3 is a polymer which has defied structure analysis, but in view of its higher melting point, it may have a cross-linked structure.

The liquid phase is an equilibrium mixture of monomer and trimer. Walrafen and Young,[2] from Raman spectra observations, suggest that about 20% exists as trimer at 25°. This, however, should be compared with the claim of Gillespie [3] and his co-workers that liquid sulphur trioxide consists mainly of the trimer at room temperature.

The gas phase is entirely monomeric at high temperatures and normal pressures. At low temperatures, the degree of association in the saturated vapour is relatively slight.

The varying states of molecular aggregation of sulphur trioxide are not unexpected when one considers the isoelectronic analogues, such as the metaphosphate ion, PO_3^-, and the metasilicate ion, SiO_3^{2-}. These also exist as cyclic trimers, *e.g.*, $(Si_3O_9)^{6-}$, as well as in polymeric chains and cross-linked structures. It is noteworthy that there is no evidence for the existence of sulphur trioxide in larger ring structures, such as exist in the 8-membered ring $(P_4O_{12})^{4-}$ or the 12-membered ring $(Si_6O_{18})^{12-}$.

Precise physicochemical measurements on the condensed phases of sulphur trioxide have undoubtedly been hindered by its ready polymerisation at room temperature, a polymerisation which is catalysed by traces of moisture and which may occur to varying and uncertain extent. The inhibition of this polymerisation has recently been reviewed by Bevington and Pegler.[1] The considerable work reported in the patent literature is largely empirical.

The present study was undertaken to investigate the mechanism of polymerisation of liquid sulphur trioxide, but uncertainties were immediately apparent about the physical properties of the liquid state. Preliminary work was therefore carried out on the vapour pressure and viscosity of the liquid.

Experimental

The sulphur trioxide was supplied in 200-g. sealed glass ampoules by the Imperial Smelting Corporation, and had been prepared by a double distillation from oleum to which a little

[1] Bevington and Pegler, *Chem. Soc. Special Publ.*, 1958, no. 12, 283.
[2] Walrafen and Young, *Trans. Faraday Soc.*, 1960, **56**, 1419.
[3] Gillespie and Oubridge, *Proc. Chem. Soc.*, 1960, 308.

potassium permanganate had been added to remove sulphur dioxide. Chemical analysis of the samples supplied showed less than 0·05% of dioxide, and after distillation *in vacuo* as described below, the content of dioxide was reduced to less than 0·005%. The amount of water present is much more uncertain since the quantitative determination of traces of moisture in sulphur trioxide is very difficult. It is generally accepted that some indication of the dryness of sulphur trioxide is given by its stability towards polymerisation.[1] The procedure described below produced final samples which could be frozen, and remelted at room temperature, two or three times before polymerisation occurred. This is a relatively high stability (in the absence of any added inhibitor) and must imply a correspondingly low moisture content; certainly $<0·1\%$ and possibly $<0·01\%$.

Purification and handling of the sulphur trioxide was carried out in a vacuum system in which the sulphur trioxide was never in contact with any material except glass. The apparatus and the subsequent purification procedure were very similar to those of Smits and Schoenmaker.[4] The apparatus was baked out at 10^{-5} mm., and then the sulphur trioxide was triply distilled *in vacuo*, only the middle fraction of each distillation being collected. The weight of the final purified sample was 10—20 g. (from 200 g.).

Vapour pressures were determined with a glass-spiral Bourdon gauge which was used as a null device and was capable of detecting a pressure difference of 0·1 mm. Viscosity measurements were made with a sealed-capillary tube viscometer, so designed that submerged discharge from the capillary was obtained. Times of flow were reproducible to $\pm 0·1\%$, and there was no apparent kinetic correction. The viscometer was calibrated with water and the calibration checked against two other liquids. For all measurements, temperature control was achieved with a thermostatic water-bath and the temperature was measured to $\pm 0·02°$ C.

t	p (mm.)	η (cp.)	L (kcal./mole)
17°	165	2·458	
20	197	2·185	10·47
25	265	1·820	10·31
30	353	1·524	10·16
35	468	1·288	10·01
40	608	1·103	9·86
45	787	0·944	9·71
50	992		9·57

These values of vapour pressure and viscosity are experimental values interpolated without "smoothing" to the exact temperature stated. Experimental measurements were always made within 0·2° of these temperatures.

Vapour Pressure.—Over forty values of the vapour pressure were recorded in the range 17—56° with temperature rising and falling. After allowance for temperature equilibration at any one temperature, there was no change of vapour pressure with time. This confirms the results of previous workers that the equilibrium between monomer and trimer in the liquid is established rapidly. The liquid remained clear and free from polymer throughout the period.

The plot of the two-constant Clausius–Clapeyron equation, $\log p = a - b/T$, showed a negative value of db/dT. The results were therefore fitted to the three-constant Antoine equation, and the constants calculated by the method recommended by Thompson.[5] The vapour pressure at t° C is given by:

$$\log_{10} p \text{ (mm.)} = 7·8663 - 1158·9/(t + 188·00)$$

The average deviation of the experimental values from this equation is $\pm 0·4\%$. This deviation is equivalent to errors in the pressure measurement varying from 0·6 mm. at the lower to 5 mm. at the higher pressures, or errors in the temperature measurement of 0·1°.

These errors are somewhat greater than expected, but a check of the above equation by a plot of the deviation curve did not show continuous "drift," or "bowing," or completely random scatter. In fact the deviation curve was of a cyclic form, showing zero deviation at about 20°, 32°, and 50° and maxima of opposite sign at intermediate temperatures.

The normal boiling point interpolated from these vapour-pressure values is $44·45 \pm 0·15°$ C.

Previous measurements of the vapour pressure in this temperature range have been reported

[4] Smits and Schoenmaker, *J.*, 1924, **125**, 2554.
[5] Thompson, *Chem. Rev.*, 1946, **38**, 1.

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by Berthoud,[6] Smits and Schoenmaker,[4] Grau and Roth,[7] and Miles, Niblock, and Wilson.[8] No two sets of results show consistent agreement, differences of 20 mm. at any one temperature being not uncommon. Our values at any given temperature almost always lie between the extremes of values previously reported. All the above workers fitted their results to a two-constant vapour-pressure equation, and in all cases the average deviations from their reported equations are greater than $\pm 1\%$.

Latent Heat.—Values of the latent heat of evaporation at 5° intervals were calculated by application of the Clapeyron equation and use of the vapour-pressure equation above. Thus,

$$L = \Delta z \, \boldsymbol{R} T^2 \, (\mathrm{d}\ln p/\mathrm{d}T) = \Delta z \, (4{\cdot}5757)(1158{\cdot}9)\, T^2/(t + 188)^2 \text{ cal./mole}$$

where $\Delta z = (pV_g/\boldsymbol{R}T) - (pV_l/\boldsymbol{R}T)$ and V_g and V_l are the molal volumes of saturated vapour and liquid, respectively. V_g was calculated from the Berthelot equation of state by using Berthoud's [6] values of the critical constants, $p_c = 83{\cdot}8$ atm., $T_c = 491°$ K. Values of Δz decreased from 0·992 at 20° to 0·978 at 50°.

The only calorimetric measurement of the latent heat is that of Grau and Roth [7] who reported a value of 10 kcal. at the normal boiling point with the admitted possibility of a large experimental error. Miles, Niblock, and Smith [10] made much more precise calorimetric determinations of the heat of evaporation of sulphur trioxide from high-strength oleums at 30° and found a limiting value of 10·3 kcal./mole at high concentrations of sulphur trioxide.

The temperature coefficient of the latent heat at 25° c being considered, $\mathrm{d}L/\mathrm{d}T \approx C_p$ (gas) $- C_p$ (liquid) $= -31$ cal. deg.$^{-1}$ mole^{-1}; the value for sulphur trioxide (gas) [9] being taken as $C_p = 12$ cal. deg.$^{-1}$ mole^{-1} (which assumes no association in the gas phase) it follows that for sulphur trioxide (liquid) at 25°, $C_p = 43$ cal. deg.$^{-1}$ mole^{-1}.

There is no reported calorimetric measurement of the specific heat of liquid sulphur trioxide, but Miles, Niblock, and Smith [10] measured this quantity for oleums of varying content of trioxide, and extrapolation of their results to 100% sulphur trioxide gives a value of *ca.* 60 cal. deg.$^{-1}$ mole^{-1}. Acceptance of this higher figure would imply that our results underestimate the decrease of latent heat with rise in temperature.

In view of this discrepancy and of the uncertainty in estimation of the volume of the saturated vapour if there is slight association, it is difficult to assess the possible error in our calculated values of latent heat. However, in the absence of precise calorimetric measurements, we feel that our values are more reliable than any previously reported.

Viscosity.—Values of the absolute viscosity were determined at 5° intervals in the range 17—50° c. There was no indication of change of viscosity with time at any temperature, nor was there any trace of polymer at any time during the measurements. The density values used to calculate the absolute viscosities were the mean of those of Berthoud [6] and of Lichty.[11]

The following equation expressed the viscosity at T °K:

$$\log_{10} \eta \text{ (cp.)} = -1{\cdot}3726 - (404{\cdot}82)T^{-1} + (2{\cdot}6583)10^5 T^{-2}$$

The average deviation of experimental values from this equation is $\pm 0{\cdot}15\%$, which is within the estimated experimental error.

Previous measurements of the viscosity of liquid sulphur trioxide have been reported by Luchinskii,[12] and by Amelin, Illarionov, and Borodastova.[13] The results of the former are far too high because of inadequate purification of the sample. The agreement between our results and those of Amelin *et al.*, who used a vacuum-distillation technique, is within 0·5% at the lower temperatures and within 2% at 50°, our figures being generally higher, though the results of the Russian workers show more " scatter."

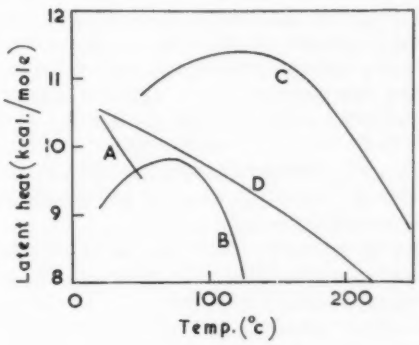
Amelin *et al.*[13] commented on the fact that a plot of log η against $1/T$ was not linear, and our findings confirm this. On the basis of the simple equation, $\eta = A \exp(E/\boldsymbol{R}T)$, this can be interpreted in terms of a variation of E with temperature. At the normal boiling point, it

[6] Berthoud, *Helv. Chim. Acta*, 1922, **5**, 513.
[7] Grau and Roth, *Z. anorg. Chem.*, 1930, **188**, 173.
[8] Miles, Niblock, and Wilson, *Trans. Faraday Soc.*, 1940, **36**, 345.
[9] Stockmayer, Kavanagh, and Mickley, *J. Chem. Phys.*, 1944, **12**, 408.
[10] Miles, Niblock, and Smith, *Trans. Faraday Soc.*, 1944, **40**, 281.
[11] Lichty, *J. Amer. Chem. Soc.*, 1912, **34**, 1440.
[12] Luckinskii, *Zhur. fiz. Khim.*, 1938, **12**, 280.
[13] Amelin, Illarionov, and Borodastova, *Zhur. fiz. Khim.*, 1951, **25**, 542.

can be calculated that $E = 5{\cdot}79$ kcal./mole and the ratio $L/E = 1{\cdot}68$. The low value of this ratio is consistent with the view that sulphur trioxide is an associated liquid.

Discussion

Latent Heat of Evaporation of an Associated Liquid.—The latent heat of evaporation of sulphur trioxide shows a marked decrease with rise in temperature and is certainly not constant as was suggested by Smits and Schoenmaker. With a normal liquid the latent heat decreases continuously with rise in temperature, becoming zero at the critical point. A substance which is associated in the liquid and the vapour phase will not necessarily exhibit this continuous decrease and the latent heat may pass through a maximum. Dinitrogen tetroxide and acetic acid both provide examples of maxima in the latent heats of evaporation, as shown in the Figure. These curves have been calculated by application of the Clapeyron equation to the recorded vapour-pressure and specific-volume data.[14] The curve for water is shown for comparison.



Variation of latent heat of evaporation with temperature.
A, *Sulphur trioxide.*
B, *Dinitrogen tetroxide.*
C, *Acetic acid dimer.*
D, *Water.*

The form of these curves is readily explicable in terms of the changing degrees of molecular association in the two phases. Consideration of an isothermal cycle involving the associated and dissociated species in both phases, as described by Gray and Rathbone [15] for dinitrogen tetroxide, gives for the latent heat of evaporation per formula weight of associated species:

$$L = L_n + \alpha\Delta H_g - \beta\Delta H_l$$

L_n is the hypothetical latent heat of evaporation of the fully associated liquid to give a fully associated vapour, ΔH_g and ΔH_l are the enthalpies of dissociation and α and β the degrees of dissociation in the vapour and the liquid phase, respectively.

Therefore at temperatures where the liquid is largely associated but the vapour is becoming increasingly dissociated a positive temperature coefficient of the latent heat may be observed, as shown by dinitrogen tetroxide and acetic acid in the lower temperature region; whereas in the case of a largely-dissociated vapour in equilibrium with an increasingly dissociated liquid, a large negative temperature coefficient will result, as in the case with sulphur trioxide at 25° and with the above two liquids at higher temperatures.

Vapour Pressure of an Associated Liquid.—Deviations from the two-constant vapour-pressure equation, $\ln = a - b/T$, can be discussed in terms of db/dT where $b = L/\Delta z$ the symbols having the same significance as before. For normal liquids at low vapour

[14] Reamer and Sage, *Ind. Eng. Chem.*, 1952, **44**, 185 (for dinitrogen tetroxide); Timmermans, "Physicochemical Constants of Pure Organic Compounds," Elsevier, London, 1950 (for acetic acid).
[15] Gray and Rathbone, *J.*, 1958, 3550.

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pressures, db/dT must always be negative, but at high pressures when both gas non-ideality and the volume of the liquid phase become increasingly significant, experiments show that for some liquids db/dT becomes positive. This effect is indicated by a point of inflection in a plot of the two-constant equation as the critical point is approached.[16] Most empirical vapour-pressure equations (including the Antoine equation) cannot represent such behaviour, and caution is always necessary in the " smoothing " of experimental measurements of high vapour pressures.

Superficial consideration of the vapour pressure of a substance which is associated in the vapour phase might lead to the expectation of even larger deviations from the two-constant equation. Application of the ideal gas equation to the saturated vapour would be manifestly incorrect if the degree of dissociation is changing with temperature. However, such an effect would also be reflected in the increase of latent heat with temperature so that db/dT would not be abnormally large, and experiment confirms that the two-constant equation is still a reasonable approximation in these cases.

These considerations are relevant to any assessment of the reliability of literature values of the vapour pressure of sulphur trioxide at higher temperatures. Above 60° the only recorded measurements are those of Smits and Schoenmaker [17] up to 90°, and of Berthoud [6] from 98° to the critical temperature, 218°. There are marked discrepancies between the two sets even though no overlapping occurs. For example, extrapolation of Smits and Schoenmaker's results gives a vapour pressure of 10·5 atm. at 98·2° compared with Berthoud's observed value of 9·2 atm. In addition, Smits and Schoenmaker's results apparently fit the two-constant vapour-pressure equation with only random scatter in the range 17—90°, whereas Berthoud's values in the range 98—218° give a definite positive value of db/dT, an effect which would necessitate a marked point of inflection in a plot of the two-constant equation.

The only recorded values for the critical pressure and critical volume are those of Berthoud.[6] Schenk [18] however measured the critical temperature and his value agrees with that of Berthoud to within 2°. It is obvious that confirmatory values are required for the vapour pressure of sulphur trioxide at high temperatures and for the critical constants, and an apparatus for that purpose is now under construction.

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[16] Reid and Sherwood, " The Properties of Gases and Liquids," McGraw-Hill, New York, 1958, p. 72.
[17] Smits and Schoenmaker, *J.*, 1926, 1108.
[18] Schenk, *Annalen*, 1901, **316**, 1.

457. *Isopropenyl and Isopropylidene Groups: The Terpene Problem.*

By T. Oliver.

Dehydration of 2-methylnonadecan-2-ol and 2-methylnonan-2-ol gave, in each case, a mixture of the isopropylidene and isopropenyl isomer. The isopropylidene form always predominated. A chemical separation of the isopropylidene isomers was developed and the isopropenyl isomers were synthesised. The C_{10} olefin mixture was separated by gas–liquid chromatography.

The structural problem of the simple natural acyclic monoterpenes [1] has recently been solved [2] with the aid of infrared spectra,[3] which showed that they exist almost entirely in the isopropylidene form. As the two isomers have not been studied side by side, attention was directed first to 2-methylnonadec-1-ene and 2-methylnonadec-2-ene and later to the corresponding C_{10} compounds.

Messer [4] regarded the dehydration product of 2-methylnonadecan-2-ol as 2-methylnonadec-1-ene alone, whereas other workers [5] found it to be solely 2-methylnonadec-2-ene. In the present study, dehydration of this tertiary alcohol was found to give a mixture of the two isomers. Quantitative infrared-absorption measurements on the carbon disulphide solution indicated that mixtures prepared by different routes contained more than 50% of the isopropylidene form.

Attempts to use physical methods to effect separation all failed as did several chemical methods. However, a chemical method of separation was developed based on the action of mercuric acetate.[6] The mixture was heated to 50—70° in propionic acid containing a small amount of mercuric acetate. The isopropenyl isomer was preferentially attacked, the course of the reaction being followed by the diminution of the strong 890 $cm.^{-1}$ infrared band. 2-Methylnonadec-1-ene was prepared by the action of hexadecylmagnesium iodide on 2-methylallyl chloride. Neither of the pure olefins showed any tendency towards interconversion when treated with cold dilute acid or alkali, or passage over alumina and distillation at 190°/10 mm. On the other hand, fairly rapid polymerisation occurred when thin layers of the olefins were exposed to air.

Dehydration of 2-methylnonan-2-ol with iodine gave a mixture, containing 70% of the isopropylidene isomer. It was not possible to prepare a sample containing more than 93% of the isopropylidene form because, in this case, it also reacted with the mercuric acetate. 2-Methylnon-1-ene was prepared in 40% yield by the Wittig–Schöllkopf reaction.[7] Again, no tendency towards interconversion was noticed. A gas–liquid chromatographic investigation of the $C_{10}H_{20}$ mixture showed that a sharp separation could be achieved by using a column of benzylbiphenyl (15%) on Embacil at 60°. The isopropylidene isomer was eluted first; the relative retention times were 85 : 89. As Howard and Stevens [8] found evidence of thermal isomerisation of some terpenoid compounds during gas–liquid chromatographic investigations, several runs were carried out with different temperatures of the inlet heater. Even with a temperature of 300°, however, there was no evidence of isomerisation.

[1] Simonsen and Owen, "The Terpenes," University Press, Cambridge, 1947, Vol. I.
[2] Caldwell and Jones, *J.*, 1946, 599; Thompson and Whiffen, *J.*, 1948, 1412; Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915.
[3] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1958, p. 34.
[4] Messer, *Chem. News*, 1929, **138**, 292; *Chem. Zentr.*, 1929, II, 1645.
[5] (*a*) Grimshaw, Guy, and Smith, *J.*, 1940, 68; (*b*) Boelhouwer, Tien, and Waterman, *Rec. Trav. chim.*, 1954, **73**, 143.
[6] Balbiano and Paolini, *Ber.*, 1903, **36**, 3575; Balbiano, *ibid.*, 1909, **42**, 1502.
[7] Wittig and Schöllkopf, *Ber.*, 1954, **87**, 1318; Levisalles, *Bull. Soc. chim. France*, 1958, 1021; Schöllkopf, *Angew. Chem.*, 1959, **71**, 260.
[8] Howard and Stevens, *J.*, 1960, 161.

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The chemical method of separation here developed, together with the chromatographic separation, should prove to be of value in studies of the natural terpenes.

Experimental

The alumina was "Activated Alumina Type 'H'" supplied by Peter Spence and Sons Limited. All infrared spectra (except those of carbon disulphide solutions) were recorded on a Perkin-Elmer "Infracord" model 137; carbon disulphide solutions were measured on a Perkin-Elmer model 21 double-beam spectrophotometer.

Preparation of 2-Methylnonadecan-2-ol.—Stearic acid (m. p. 67·5—69·5°) and pure methanol yielded the ester which, after fractional distillation and recrystallisation from acetone, had m. p. 38—39°. In the preparation of the alcohol,[9] it was advantageous to use 4 mol. of methylmagnesium iodide to 1 mol. of ester. Recrystallisation from light petroleum (b. p. 40—60°) at −8° gave 2-methylnonadecan-2-ol (81%), m. p. 45·5—46·5° (Smith [5a] gave m. p. 45·5°; Ryan and Dillon,[9] 44—45°).

Preparation of the Mixture of Eicosenes.—(*a*) 2-Methylnonadecan-2-ol (33 g.) and resublimed iodine (0·17 g., 0·5%) were heated for 2 hr. under dry carbon dioxide at 150°. The reaction product distilled at 186—192°/9·3 mm. and was refluxed with excess of acetic anhydride for 30 min. Excess of anhydride was distilled and the residue boiled at 192—196°/9 mm. The olefin mixture had m. p. 12·5—13·3°, n_D^{20} 1·4515, iodine no. 90·4 (theory 90·5), $\nu_{max.}$ 890s and 833m cm.$^{-1}$. The infrared spectrum of a solution in carbon disulphide indicated 65% of the isopropylidene form.

(*b*) 2-Methylnonadecan-2-ol (4 g.) was heated to 115—120° and hydrogen bromide was then passed through for 30 min. The mixture was cooled and extracted with ether. The extracts were dried (Na_2SO_4) and evaporated. Recrystallisation of the residue from hexane afforded 2-bromo-2-methylnonadecane (84%), m. p. 20·0—20·7°. 2-Bromo-2-methylnonadecane (2·6 g.) and redistilled quinoline (2·3 ml.) were heated for 1 hr. at 160° ± 5° under nitrogen. Excess of quinoline was removed and the residue allowed to cool. The upper layer was poured into water and the whole extracted with ether. The extracts were washed with 2N-hydrochloric acid, and water, dried (Na_2SO_4), and evaporated. The residue distilled at 190—194°/10 mm. to give the olefin mixture, m. p. 13·4—14·1°, n_D^{20} 1·4508, $\nu_{max.}$ 890s and 833m cm.$^{-1}$. The infrared spectrum of a solution in carbon disulphide indicated 52% of the isopropylidene isomer.

Separation of 2-Methylnonadec-2-ene.—The olefin mixture (2·2 g.; m. p. 12·5—13·3°) and mercuric acetate (0·13 g., 5% stoicheiometric weight) in propionic acid (40 ml.) were heated for 30 min. at 65—70°. 10 ml. of the hot solution were poured into water (30 ml.), and the upper layer was extracted with light petroleum (b. p. 60—80°). After being dried (Na_2SO_4), the ether extracts were passed through alumina, and yielded an olefin mixture which after distillation had m. p. 11·9—12·4°. The peaks at 890 and 833 cm.$^{-1}$ showed the same percentage absorption. This procedure was repeated twice (0·03 g. of acetate; 65—70°; 30 min.) giving an olefin mixture of m. p. 11·5—12·3°. The peak at 833 cm.$^{-1}$ was now stronger than that at 890 cm.$^{-1}$. The remaining 10 ml. with the usual procedure (0·02 g. of acetate; 50—55°; 30 min.) gave a mixture, m. p. 10·5—11·3°. This mixture was taken up in propionic acid (10 ml.), and the separation procedure (0·02 g. acetate; 50°; 30 min.) gave 2-methylnonadec-2-ene, m. p. 9·0—10·2°, n_D^{20} 1·4524, $\nu_{max.}$ 833 cm.$^{-1}$. The infrared spectrum of a solution in carbon disulphide showed no peak at 890 cm.$^{-1}$.

Preparation of 2-Methylnonadec-1-ene.[10]—Cetyl iodide (12 g.; m. p. 24·0—24·6°) in dry ether (70 ml.) was added slowly to magnesium turnings covered with dry ether (60 ml.) under normal Grignard conditions. Some white solid separated (later shown to be dotriacontane). 2-Methylallyl chloride (6·2 g.; b. p. 71·7—72·2°; 100% excess) in dry ether was then added and the mixture stirred for 5 hr. at room temperature. The complex was decomposed with water and then with dilute hydrochloric acid, and the whole extracted with ether. After the dotriacontane had been filtered off, the extracts were washed with 2N-hydrochloric acid, water, and 2N-sodium carbonate, dried (Na_2SO_4), and evaporated. The residue was repeatedly fractionally distilled until the higher-boiling fractions gave a negative Beilstein halogen test. These fractions were then adsorbed on alumina, and elution with light petroleum (b. p. 60—80°) gave 2-methylnonadec-1-ene (5%), m. p. 12·7—13·1°, n_D^{20} 1·4495, $\nu_{max.}$ 890s cm.$^{-1}$.

[9] Ryan and Dillon, *Proc. Roy. Irish Acad.*, 1912, **29**, *B*, 235.
[10] Tiffeneau, *Bull. Soc. chim. France*, 1903, **29**, 1157; *Compt. rend.*, 1904, **139**, 481.

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Preparation of 2-Methylnonan-2-ol.—Pure methanol and octanoic acid (m. p. 14·5—16·7°) yielded the ester which, after fractional distillation, had b. p. 90°/20·3 mm. (lit.,[11] 83°/15 mm.). Methyl octanoate (50 g.) in ether (40 ml.) was added dropwise to a solution of methylmagnesium iodide in ether under normal Grignard conditions. The complex was decomposed with water, then with 2N-sulphuric acid, and the whole extracted with ether. The combined extracts were washed with 2N-sodium carbonate and with water, dried (Na_2SO_4), and evaporated. The residue in ethanol was then refluxed with potassium hydroxide (10 g.) in water (70 ml.) for several hours, poured into water, and extracted with ether. After being washed with water, the extracts were dried (Na_2SO_4) and evaporated. Fractional distillation of the residue gave 2-methylnonan-2-ol (70%), b. p. 101·0—101·8°/21·6 mm. (lit.,[12] 96—98°/13·5 mm.), n_D^{20} 1·4320, $\nu_{max.}$ 725s, 769s, 909s, 952s, 1075m, 1105m, 1149s, 1190s, 1370s, 1460s, 2857s, 2924s, and 3333s cm.$^{-1}$ (Found: C, 75·7; H, 13·7. Calc. for $C_{10}H_{22}O$: C, 75·9; H, 14·0%). The *α-naphthylurethane* (after 432 hr. at room temperature), recrystallised from aqueous alcohol, had m. p. 70·0—70·8° (Found: C, 77·1; H, 9·0; N, 4·4. $C_{21}H_{29}NO_2$ requires C, 77·0; H, 8·9; N, 4·3%).

Preparation of the Mixture of Decenes.—2-Methylnonan-2-ol (26 g.) and resublimed iodine (0·15 g., 0·5%) were heated for 2 hr. at 150° under nitrogen. An ethereal solution of the distilled crude mixture was washed with 2N-sodium hydroxide and with water, dried (Na_2SO_4), and evaporated. The residue distilled at 64·7—66·5°/20 mm. to give the olefin mixture, n_D^{20} 1·4272, $\nu_{max.}$ 890s and 833m cm.$^{-1}$. The infrared spectrum of a solution in carbon disulphide indicated 70% of the isopropylidene isomer.

Separation of 2-Methylnon-2-ene.—The olefins (14 g.) and mercuric acetate (3 g.) in propionic acid (30 ml.) were heated for 30 min. at 65—70°. On cooling, black mercury and mercurous salts were deposited. The solution was poured into water (100 ml.) and the unchanged olefins extracted with light petroleum (b. p. 40—60°). The extracts were washed with 2N-sodium carbonate, and water, dried (Na_2SO_4), and adsorbed on an alumina column. Evaporation of the light petroleum eluate gave unchanged olefin mixture. This procedure was repeated 10 times, the amount of acetate being progressively reduced to 0·1 g.; a temperature of 50° was used in the last 3 separations. The final sample had b. p. 164—166°/757 mm., n_D^{20} 1·4286 [lit.,[13] n_D^{20} (calc.) 1·4289, b. p. (calc.) 169·9°/760 mm.]. The infrared spectrum of a solution in carbon disulphide showed a very small peak at 890 cm.$^{-1}$ and indicated 93 ± 2% of the isopropylidene isomer. It was found impossible to increase the percentage of the isopropylidene isomer by this procedure.

Preparation of 2-Methylnon-1-ene.[7]—Lithium (1·4 g., 0·2 g.-atom) was added gradually to bromobenzene (10 g. 0·06 mol.) in ether (100 ml.) under nitrogen. After reaction had finished, the phenyl-lithium solution was filtered into a stirred suspension of methyltriphenylphosphonium iodide (25·5 g., 0·06 mol.) in ether (200 ml.), and the whole stirred under nitrogen for 2·5 hr. at room temperature. Heptyl methyl ketone [14] (3 g.; 0·02 mol.; m. p. −7·4°) was added during 15 min. The mixture was then heated on a water-bath, light petroleum being added, as the ether distilled, to give a refluxing temperature of 64—66°. After refluxing for 5 hr., the solution was cooled, filtered, and passed through alumina. Evaporation of the light petroleum (b. p. 60—80°) eluate gave 2-methylnon-1-ene contaminated with bromobenzene. The crude olefin was readsorbed on alumina; elution with light petroleum (b. p. 40—60°) gave a first olefin-containing fraction which gave a negative Beilstein halogen test. The olefin had b. p. 68—70°/25·5 mm., n_D^{20} 1·4249 (lit.,[15] b. p. 66·23°/20 mm., n_D^{20} 1·42409). Further fractions afforded olefin containing 3—4% of bromobenzene, n_D^{20} 1·4286. The yield was 40%.

Gas-chromatography Experiments.—The column was benzylbiphenyl (15% on Embacil; May and Baker Ltd.). Its length was 400 cm. and diameter 4·5 mm. The temperature of the column was 60°. The carrier gas was hydrogen, and the flow rate was 39 ml./min. The inlet pressure was 1330 mm. The detector was a flame-ionization detector [16] modified as by Thompson.[17] The recorder was a Honeywell–Brown recorder, and a flame-ionization current

[11] Haller and Yousouffian, *Compt. rend.*, 1906, **143**, 805.
[12] Houben, *Ber.*, 1902, **35**, 3589.
[13] Mears, Fookson, Pomerantz, Rich, Dussinger, and Howard, *J. Res. Nat. Bur. Stand.*, 1950, **44**, 299.
[14] Shenton and Smith, *Chem. and Ind.*, 1958, 1510.
[15] Schuhmacher, Wibaut, and Paerels, *Rec. Trav. chim.*, 1953, **72**, 1037.
[16] McWilliam and Dewar, *Nature*, 1958, **181**, 760.
[17] Thompson, *J. Chromatog.*, 1959, **2**, 148.

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of 5×10^{-10} amp. gave full-scale deflection. The temperature of the inlet heater was 150—200°. Under these conditions, the isopropylidene isomer was eluted after 85 min., the isopropenyl isomer after 89 min. In view of Howard and Stevens's [8] results, experiments were carried out with inlet-heater temperatures of 45°, 100°, 150°, 200°, and 300°. In all cases, the proportions of the isomers were unchanged.

The author is indebted to Dr. J. C. Smith for suggesting the problem, for helpful discussions and constant encouragement, to Dr. G. D. Meakins and his staff for infrared-spectra determinations, and to Mr. A. E. Thompson for the gas-chromatography determinations.

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458. *Molecular Polarisability. Electric Double Refraction of Solutions containing Optically Active Solutes.*

By J. M. ECKERT and R. J. W. LE FÈVRE.

The possibility of measuring the electric double refraction of optically active compounds in dilute solution is examined by comparing results obtained for (±)-solutes with those for their (+)- or (−)-isomers. Molar Kerr constants are reported for inactive and active camphor, camphorquinone, diethyl tartrate, and *N*-benzoylamphetamine; at infinite dilution the values for each pair of isomers differ only by amounts which are within the range of experimental errors often experienced in such determinations.

OUR standard arrangement [1,2] for measuring the electric birefringence of a solution requires the latter to be traversed by a ray of light plane-polarised at 45° to a transverse electric field. The solution is placed between Nicol prisms, crossed for extinction before application of the field. Phase differences are determined with the compensator described by Szivessy and Dierkesmann.[3] Two difficulties can be foreseen if the solution possesses natural optical rotatory power: (*a*) the field-polarisation angle will vary continuously as the light passes through the field, and (*b*) extinction under zero-field conditions will no longer involve polariser–analyser settings of $\pm\pi/2$ as required by the formulæ given in ref. 3. Of these, (*a*) is the more serious since it implies that the doubly refracting solution is not in the fixed azimuths $\pm\pi/4$, as normally used with optically inactive media, and that the maximum Kerr effect (induced by a field-polarisation angle of 45°) cannot be displayed by the liquid under examination. Since these considerations threaten the applicability of electric birefringence measurements to stereostructural questions concerning optically active substances, and since the assessment of their effects from *a priori* theory is complex, the problem has been approached experimentally.

EXPERIMENTAL

General.—Apparatus, procedures, symbols, and methods of calculation are as described or defined in refs. 1, 2, and 4. Contexts should prevent confusion between α, our usual symbol for the dielectric constant increment of a solution, and the conventional symbol of rotatory power.

Solvents.—These have been freshly-distilled calcium chloride-dried carbon tetrachloride or sodium-dried benzene, to which the following physical constants apply:

	ε	d_4^{25}	n_D^{25}	10^7B
Carbon tetrachloride	2·2270	1·5845	1·4575	0·070
Benzene	2·2725	0·87378	1·4973	0·410

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[1] Le Fèvre and Le Fèvre, *Rev. Pure Appl. Chem.* (*Australia*), 1955, **5**, 261.
[2] Le Fèvre and Le Fèvre, (*a*) *J.*, 1953, 4041; (*b*) *J.*, 1954, 1577.
[3] Szivessy and Dierkesmann, *Ann. Physik*, 1931, **11**, 949; *Z. Instrumentenkunde*, 1932, **52**, 337.
[4] Le Fèvre, "Dipole Moments," Methuen, London, 3rd Edn., 1953.

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TABLE 1. *Kerr effects, dielectric constants, etc., for solutions in carbon tetrachloride or benzene at 25°.*

(+)-Camphor in carbon tetrachloride

10^5w_2	502	626	700	899	1021	1111	1473	1586	1617	1816
ε^{25}	2·2872	2·3036	2·3100	2·3340	2·3460	2·3599	2·4006	2·4145	2·4177	2·4411
d^{25}	1·57930	1·57837	1·57731	1·57618	1·57416	1·57313	1·56975	1·56861	1·56827	1·56659
Δn	0·0002	0·0002	0·0002	0·0004	0·0004	0·0005	—	0·0005	0·0007	0·0010

whence $\Delta\varepsilon = 12{\cdot}01_5w_2 - 13{\cdot}34w_2^2$, $\Sigma\Delta d/\Sigma w_2 = -1{\cdot}002$, $\Sigma\Delta n/\Sigma w_2 = 0{\cdot}042$

10^5w_2	122	164	220	350	422	624
$10^7\Delta B$	0·008	0·012	0·020	0·033	0·041	0·066

whence $10^7\Delta B = 7{\cdot}42w_2 + 530w_2^2$

(−)-Camphorquinone in carbon tetrachloride

10^5w_2	281	349	393	484	578	706	900
ε^{25}	2·2909	2·3105	2·3226	2·3448	2·3568	2·3957	2·4412

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 23{\cdot}67$

10^5w_2	175	314	411	516	665	793	897
d^{25}	1·58329	1·58209	1·58133	1·58044	1·57950	1·57830	1·57794
Δn	0·0002	0·0002	0·0004	0·0004	0·0005	0·0006	0·0006

whence $\Sigma\Delta d/\Sigma w_2 = -0{\cdot}766$, $\Sigma\Delta n/\Sigma w_2 = 0{\cdot}077$

10^5w_2	29	58	84	151	293
$10^7\Delta B$	0·004	0·010	0·015	0·030	0·066

whence $10^7\Delta B = 16{\cdot}96w_2 + 1875w_2^2$

(±)-Camphorquinone in carbon tetrachloride

10^5w_2	163	290	467	763	908
$10^7\Delta B$	0·025	0·054	0·084	0·125	0·159

whence $\Sigma\Delta B/\Sigma w_2 = 17{\cdot}25 \times 10^{-7}$

Diethyl (+)-tartrate in carbon tetrachloride

10^5w_2	386	775	1057	1222	1689	2519
ε^{25}	2·2653	2·3016	2·3315	2·3455	—	2·4618
d^{25}	1,58215	1·58043	1·57859	1·57743	1·57512	1·57056
Δn	−0·0002	−0·0003	−0·0004	−0·0004	−0·0005	−0·0008

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 9{\cdot}57$, $\Sigma\Delta d/\Sigma w_2 = -0{\cdot}562$, $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}034$

10^5w_2	245	343	422	596	750
$10^7\Delta B$	0·004	0·003	0·005	0·005	0·009

whence $\Sigma\Delta B/\Sigma w_2 = 1{\cdot}11 \times 10^{-7}$

Diethyl (±)-tartrate in carbon tetrachloride

10^5w_2	208	412	559	803	966	2696
$10^7\Delta B$	0·003	0·005	0·006	0·009	0·010	0·026

whence $\Sigma\Delta B/\Sigma w_2 = 1{\cdot}04 \times 10^{-7}$

(−)-N-Benzoylamphetamine in benzene

10^5w_2	275	355	487	527	552	610
ε^{25}	2·2915	2·2968	2·3043	2·3068	2·3108	2·3123

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 6{\cdot}68$

10^5w_2	156	232	302	324	374	425	555	575
d^{25}	0·87420	0·87434	—	0·87440	0·87998	—	0·87482	0·87490
Δn	—	—	0·0002	0·0002	0·0004	0·0003	0·0006	0·0007

whence $\Sigma\Delta d/\Sigma w_2 = 0{\cdot}201$, $\Sigma\Delta n/\Sigma W_2 = 0{\cdot}082$

10^5w_2	292	409	418	574	597
$10^7\Delta B$	−0·004	−0·005	−0·006	−0·009	−0·009

whence $\Sigma\Delta B/\Sigma w_2 = -1{\cdot}44 \times 10^{-7}$

(±)-N-Benzoylamphetamine in benzene

10^5w_2	298	335	469	534	558
$10^7\Delta B_1$	−0·004	−0·005	−0·006	−0·009	−0·009

whence $\Sigma\Delta B/\Sigma w_2 = -1{\cdot}49 \times 10^{-7}$

Solutes.—These were recrystallised or redistilled just before use. (−)-Camphorquinone was prepared by oxidation [5] of (+)-camphor under reflux with selenium dioxide for 3—4 hr. Filtration, precipitation by neutralisation, and crystallisation from light petroleum yielded orange needles, $[\alpha]_D = -100{\cdot}3°$ (toluene). (±)-Camphorquinone resulted from a similar treatment of (±)-camphor. Diethyl (+)-tartrate, a commercial sample of high purity (from British Industrial Solvents), after distillation at 160—162°/12—15 mm., had $[\alpha]_D = +5{\cdot}0°$. Diethyl racemate was prepared by following the directions of Vogel.[6] (+)- and (±)-Amphetamine, obtained as oils from the hydrochlorides by treatment with alkali, proved to be insufficiently soluble in either benzene or carbon tetrachloride, and were therefore converted by the Schotten–Baumann reaction [6] into the corresponding *N*-benzoyl derivatives.

Measurements.—These are listed in Table 1, and calculated quantities, including dipole moments and molar Kerr constants at infinite dilution, in Table 2.

Previous determinations. Dipole moments in Debye (D) units have been recorded (for benzene solutions at 25°, unless otherwise stated) as follows (references in parentheses):

(±)-Camphor: 2·95, (7), 22°; 2·94, (8), 22°; 3·05, (9), 20°; 2·91 (10), 20°; 3·10 (11); 3·09, (12), in CCl_4. (±)-Camphorquinone: 4·46, (13), 4·78, (14), 35°. Diethyl (±)-tartrate: 3·16, (15), 38°; 3·10, (16); 3·45, (11). Diethyl (+)-tartrate: 3·46, (11).

No molar Kerr constants for the solutes of Tables 1 and 2 are in the literature; de Mallemann [17] mentions the electric birefringence of some solutions of camphor in hexane, and Schob [18] reports the Kerr constant B of liquid ethyl (+)-tartrate from 0° to 80°, but in neither case are the data relevant to the present inquiry.

TABLE 2. *Calculation of results.*

	$\alpha\varepsilon_1$	β	γ	δ	$_\infty P_2$ (c.c.)	R (c.c.)	(μ) (D)*	$10^{12}{}_\infty(_mK_2)$
(+)-Camphor	12·02	−0·632	0·029	106	239·3	44·8	3·06	116
(±)-Camphor	12·18	−0·612	0·032	105	—	—	—	115 †
(−)-Camphorquinone	23·67	−0·484	0·053	242	461·4	46·6	4·49	289
(±)-Camphorquinone	—	—	—	246	—	—	—	294 †
Diethyl (+)-tartrate	9·58	−0·355	−0·023	15·9	260·2	45·7	3·22	19·7
Diethyl (±)-tartrate	—	—	—	14·8	—	—	—	18·0
(−)-*N*-Benzoylamphetamine	6·68	0·230	0·055	−3·5	363·2	72·8	3·74	−107
(±)-*N*-Benzoylamphetamine	—	—	—	−3·6	—	—	—	−110

* Calculated for distortion polarisation of $1{\cdot}05R_D$.

† Values of $\alpha\varepsilon_1$, β, and γ measured for optically active species were assumed to hold for the corresponding racemate within the limits of experimental error.[11]

DISCUSSION

The last column of Table 2 shows that standard procedures [1,2] for the extrapolation of observations can lead to values of molar Kerr constants at infinite dilution which, for each pair of optically active–inactive isomers, differ no more than repeated determinations on a single inactive solute sometimes do. The situation resembles that found by Le Fèvre and Maramba [11] for the total polarisations of such pairs, values of $_\infty P_2$ being the same, within the normal range of experimental error, although the rates of change with concentration of P_2 were not always identical. If the differences, ΔB, listed in Table 1, between the Kerr constants of the solutions and solvent, are plotted against w_2 for the four solute pairs

[5] Evans, Ridgion, and Simonsen, *J.*, 1934, 137.
[6] Vogel, " Practical Organic Chemistry," Longmans, London, 3rd Edn., 1956.
[7] Donle and Volkert, *Z. phys. Chem.* (*Leipzig*), 1930, *B*, **8**, 60.
[8] Wolf, *Physikal. Z.*, 1930, **31**, 227.
[9] Higasi, *Bull. Inst. Phys. Chem. Res. Tokyo*, 1932, **11**, 729.
[10] Sahney, Burucha, and Sarua, *J. Ind. Chem. Soc.*, 1948, **25**, 285.
[11] Le Fèvre and Maramba, *J.*, 1952, 235.
[12] Le Fèvre and Le Fèvre, *J.*, 1956, 3549.
[13] Le Fèvre, Maramba, and Werner, *J.*, 1953, 2496.
[14] Narasimhan, *Proc. Indian Acad. Sci.*, 1953, **37***A*, 551.
[15] Wolf, *Trans. Faraday Soc.*, 1930, **26**, 315.
[16] Wolf and Bodenheimer, *Z. physikal. Chem.*, 1931, *Bodenstein Festschrift*, 620.
[17] de Mallemann, *Ann. Physique*, 1924, **2**, 99; *Compt. rend.*, 1923, **176**, 380; **177**, 1028.
[18] Schob, *Compt. rend.*, 1934, **198**, 2232.

nder examination, points for the inactive form are in no case superior to those for the active form; in two of the instances the divergence, making $\Delta B/w_2$ less positive for the (±)- than for the (+)- or (−)- variety, clearly increases with w_2.

Since, as Table 10 in ref. 2(*b*) illustrates, errors in ${}_{\infty}({}_{m}K_2)$ are mostly due to those in δ (by which ΔB is related to w_2) it is obvious that when dealing with an optically active solute particular care must be taken with the value of ΔB for the stronger solutions, because in the process of fitting observed ΔB's by the method of least squares to the equation $(\Delta B)_{w_2} = aw_2 + bw_2^2$ the value of a, *i.e.* $b_1\delta$ for $w_2 = 0$, is sensitively affected by these larger ΔB's; even so, the technique here justified is practically simpler than that suggested by Ilberg,[19] namely, to place the Kerr cell within a solenoid and to nullify the optical rotation by a superposed Faraday effect.

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[19] Ilberg, *Physikal. Z.*, 1925, **26**, 901.

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459. *Mechanism of Electrophilic Substitution at a Saturated Carbon Atom. Part VI.* The Pattern of Steric Effects among Alkyl Groups and Mechanisms in One-alkyl Mercury-exchange.*

By E. D. HUGHES and H. C. VOLGER.

Steric retardations by alkyl groups in one-alkyl S_E2 mercury-exchanges are in the order: methyl < primary alkyl < secondary alkyl (so far as has yet been explored). Among primary alkyl groups, neopentyl is in no way special: it exerts only a slight steric retardation, closely similar to that of the ethyl group. In the example of neopentyl, steric retardations are in the mechanistic order, $S_E2 < S_Ei$-one-anion $< S_Ei$-two-anion. All these experimental findings can be plausibly understood having regard to the geometries of the relevant transition states.

IT seems axiomatic that the pattern of steric effects over any range of structures, such as that of alkyl groups, must be very different in bimolecular substitutions that retain configuration from what it is in those that produce stereochemical inversion.

It is well established that bimolecular nucleophilic substitution produces inversion; and the pattern of steric effects among alkyl groups in such reactions is known. Probably the most widely discussed high-light of that pattern is the extreme resistance of neopentyl systems to substitution, a phenomenon discovered by Whitmore [1] and later explained by Dostrovsky and Hughes,[2] who showed that it was associated with, and confined to, S_N2 processes, which, according to the stereokinetic principle that had by that time been established, passed through a configuration-inverting transition state, the geometry of which accounted for the very low kinetic reactivities.

All the S_E2 substitutions [3] of mercury for mercury, which have been identified [4-6] in the foregoing Parts of this Series, proceed with retention of configuration. As is explained

* Part V, *J.*, 1961, 1142.

[1] Whitmore and Fleming, *J. Amer. Chem. Soc.*, 1933, **55**, 4161; Whitmore, Wittle, and Popkin, *ibid.*, 1939, **61**, 1586; Whitmore, Popkin, Bernstein, and Wilkins, *ibid.*, 1941, **63**, 124.

[2] Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603; Dostrovsky and Hughes, *J.*, 1946, 157 *et seq.* (7 papers).

[3] Charman, Hughes, and Ingold, *J.*, 1959, 2523.

[4] Charman, Hughes, and Ingold, *J.*, 1959, 2530.

[5] Charman, Hughes, Ingold, and Thorpe, *J.*, 1961, 1121.

[6] Hughes, Ingold, Thorpe, and Volger, *J.*, 1961, 1133.

below, we expect for them quite a different pattern of steric effects. Neopentyl substitutions should show no strong retardations, but should resemble other primary alkyl substitutions, as of ethyl compounds. Primary alkyl, including neopentyl, substitutions should be less sterically restricted than the simplest secondary alkyl substitutions, as of isopropyl or s-butyl compounds.

In order to check the body of theoretical predictions, here partly quoted, at its most sensitive point, we examined first the uncatalysed one-alkyl substitution, by mechanism S_E2, of mercuric bromide into neopentylmercuric bromide. This work took in also the same substitution under one-anion and two-anion catalysis by bromide ion,[7] where the mechanisms at work are of S_Ei character,[3] involving geometrical situations appreciably different from those belonging to the uncatalysed substitution S_E2.

A series of experiments was first made with neopentylmercuric bromide and radiomercuric bromide in ethanol at 100·3° without a catalyst. The rate-constants thus obtained were very rough, because, before the exchanges had gone far, decomposition set in with the production of a mercurous precipitate, which, even before there was enough of it to upset the stoicheiometry, disturbed the kinetics by inducing some kind of catalysis. Knowing that mercurous decompositions are usually less troublesome in fast mercury exchanges, we thought we should get better results by measuring the substitution under catalysis by lithium bromide, and deducing the uncatalysed rate by extrapolation to zero concentration of catalyst. This proved the better route to the uncatalysed rate, besides giving parallel information about the catalysed rates. The relevant data are in Table 1.

TABLE 1. *Second-order rate-constants of substitution* ($k_2^{(1)}$ *or* $k_{2c}^{(1)}$ *in mole*$^{-1}$ *l. sec.*$^{-1}$) *of mercuric bromide* (*concentration a*), *in ethyl- or neopentyl-mercuric bromide* (*concentration b*), *either without catalysis, or in the presence of lithium bromide* (*concentration c*), *as followed by radiometric observation of mercury exchange in ethanol.*

(The radioactivity of mercury-203 was initially wholly in the inorganic mercuric salt. Reaction was followed through its progressive appearance in separated alkylmercuric salt. All concentrations and rate-constants are corrected for thermal volume changes of the solvent.)

Run	Temp.	Followed %	*a* (M)	*b* (M)	*c* (M)	$10^5k_{2c}^{(1)}$
Neopentylmercuric Bromide (*bromide-catalysed*)						
144	100·3°	14	0·091	0·092	0·0202	10·1
146	,,	16	0·091	0·092	0·0314	13·5
142	,,	10	0·091	0·092	0·0438	17·4
145	,,	29	0·094	0·093	0·063	23·0
143	,,	29	0·091	0·092	0·098	31·1
159	,,	25	0·093	0·092	0·127	34·5
158	,,	44	0·091	0·092	0·160	39·3
149	,,	40	0·091	0·092	0·188	41·8
Ethylmercuric Bromide (*uncatalysed*)						$10^5k_2^{(1)}$
153	72·9°	3	0·098	0·0262	—	0·76
152	100·2	5	0·155	0·0500	—	4·9
151	100·3	4	0·114	0·0407	—	5·8

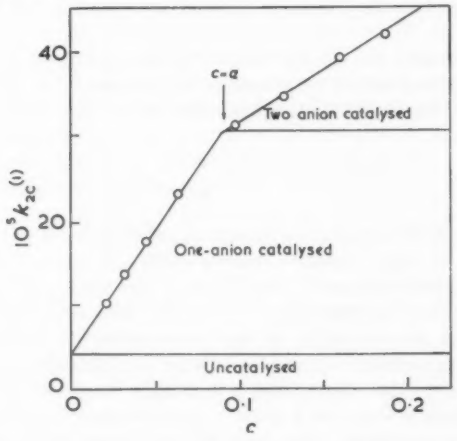
A plot of the rate-constants for the neopentyl exchange reaction is shown in the Figure, which it is interesting to compare with the analogous plot for the methyl exchange reaction, as given in Fig. 1 of Part V.[7] Both plots refer to calculated second-order rate-constants of substitution, $k_{2c}^{(1)}$, derived from the experimental rate-constants of label-transfer, κ_1, and the rates of exchange, k_0, by the relations [5] $k_{2c}^{(1)} = k_1/(a + b) = k_0/ab$; and they show these substitution rate-constants as functions of the concentration c of the lithium bromide catalyst, in a series of experiments in which the concentrations, a, of mercuric bromide, and b, of the alkylmercuric bromide, were kept constant. Both curves consist of two straight lines, meeting with a break of gradient about the point at which the concentration of lithium bromide equals that of the mercuric bromide ($c = a$). However, there are differences.

[7] Charman, Hughes, Ingold, and Volger, *J.*, 1961, 1142.

One difference relates to the intercept. In the methyl exchange, the catalysis by bromide ion is so strong that, on the scale on which the plot of rates has to be made, the curve appears to pass through the origin, the intercept representing the uncatalysed rate-constant being unreadably small—though, fortunately, that rate-constant can be measured independently and directly. In the neopentyl exchange, on the other hand, the catalysis is so far weakened that, when the rate-plot is made, the uncatalysed rate-constant appears as an easily readable intercept. We think that the value thus found, $k_2^{(1)} = 4{\cdot}2 \times 10^{-5}$ mole^{-1} l. sec.$^{-1}$, is good to about 10%.

The other notable difference relates to the change of gradient at the break. In the plot of methyl exchange, the gradient increases at that point; in the plot for neopentyl,

Dependence of the second-order rate-constant of one-alkyl substitution, $k_{2c}^{(1)}$, by mercuric bromide in neopentylmercuric bromide in ethanol at 100·3°, on the concentration, c, of added lithium bromide, the concentrations of the mercury-exchanging substances being $a = b = 0{\cdot}92$M. The curve is that of the equation on p. 2362, with $k_2^{(1)} = 4{\cdot}2 \times 10^{-5}$ mole^{-1} l. sec.$^{-1}$, $\kappa_1 = 26{\cdot}4 \times 10^{-5}$ mole^{-1} l. sec.$^{-1}$, and $\kappa_2 = 122 \times 10^{-5}$ mole^{-2} l.^{2} sec.$^{-1}$.



it decreases. In Part V,[7] where the theory of one-anion and two-anion catalysis was developed, it was noted that an increase of gradient, the only form of break that had been observed up to that time, was not required by the theory, which would allow a decrease of gradient to appear, such as that which has now been found. The difference implies that, whilst, on passing from the methyl to the neopentyl mercury-exchange, anion catalysis is generally weakened, as we have seen, yet two-anion catalysis suffers a substantially greater weakening than does one-anion catalysis.

Let us next consider more particularly the results applying to the uncatalysed one-alkyl substitution, S_E2. As we already have [6] a good value for the methyl rate, our determination of the neopentyl rate completes the comparison of main interest. However, a little filling-in is possible. We have made some approximate measurements of the ethyl rate by the direct method, which is feasible in that case. These results also are included in Table 1.* We did not attempt similar measurements of the isopropyl rate, because of

* Sintova's rates for the corresponding n-propyl exchange [8] are about twice as large as ours for ethyl, though we would have expected the rate for the higher homologue to be slightly the smaller (for entropic reasons: the activation energies should be identical). This comparison might, however, be affected by the unknown experimental cause which makes Nefedov, Sintova, and Frolov's rates, for the methyl example,[9] about 2½ times as large as the rates we recorded in Part IV [6] for that reaction in like conditions.

[8] Sintova, *Zhur. neorg. Khim.*, 1957, **2**, 1205.
[9] Nefedov, Sintova, and Frolov, *Zhur. fiz. Khim.*, 1956, **30**, 2356.

past troubles with the mercurous decomposition in the similar s-butyl case, and because we had already obtained a good comparison of methyl and s-butyl S_E2 rates in one-alkyl substitution, by going over from bromides to the faster-reacting acetates,[6] thus evading the mercurous disturbance. The figures which seem worth comparing are put together in Table 2.

TABLE 2. *Effect of alkyl structure on second-order rate-constants of substitution* ($k_2^{(1)}$ *in* $mole^{-1}$ *l. sec.*$^{-1}$) *and on relative rate in uncatalysed one-alkyl mercury-exchange*

$$RHgX + HgX_2 \rightleftharpoons RHgX + HgX_2$$

where X *is bromide or acetate, in ethanol at* 60° *or* 100°.

R	$10^5k_2^{(1)}$ Bromides at 100°	$10^5k_2^{(1)}$ Acetates at 60°	Relative rates
Methyl	12·8	500	100
Ethyl	5·4	—	42
Neopentyl	4·2	—	33
s-Butyl	—	30·9	6

We can further compare the methyl and neopentyl groups with regard to the rates of the two bromide-catalysed mercury-exchanges that proceed by mechanisms of S_Ei type. For both alkyl groups, we have experimental relations of the form,[7]

$$k_{2c}^{(1)} = k_2^{(1)} + \begin{cases} \kappa_{1(c/a)} & (c < a) \\ \kappa_1 + \kappa_{2(c-a)} & (c > a) \end{cases}$$

where the catalytic constants κ_1 and κ_2 are as entered in Table 3. The one-anion constant κ_1 has the dimensions of a second-order rate-constant. Hence the convenient measure of the strength of one-anion catalysis is the value of the dimensionless ratio $\kappa_1/k_2^{(1)}$. The two-anion constant κ_2 has the dimensions of a third-order rate-constant. Thus the most convenient measure of the strength of two-anion catalysis is the dimensionless ratio $a\kappa_2/k_2^{(1)}$. Two-anion catalysis becomes just equally strong with one-anion when $a\kappa_2 = \kappa_1$. Hence the dimensionless ratio $a\kappa_2/\kappa_1$, which is simply the ratio of the slopes of the two branches of such a curve as is in the Figure, is the best measure of the relative strengths of two- and one-anion catalysis. All these dimensionless ratios are given in Table 3.

TABLE 3. *Values and ratios for methyl and neopentyl groups of* (a) *the rate-constants,* $k_2^{(1)}$ *of the uncatalysed mercury exchanges of the alkylmercuric bromide with mercuric bromide in ethanol,* (b) *the catalytic constants,* κ_1 *and* κ_2 *of the one- and two-anion catalyses of these exchanges by bromide ion,* (c) *the dimensionless measures,* $\kappa_1/k_2^{(1)}$ *and* $a\kappa_2/k_2^{(1)}$, *of the strengths of the one- and two-anion catalyses, and* (d) *the dimensionless measure,* $a\kappa_2/\kappa_1$, *of the relative strengths of the two catalyses.*

[For methyl at 100°, a had various values; for methyl at 60°, $a = 0{\cdot}095$; for neopentyl at 100°, $a = 0{\cdot}092$M. Units: $k_2^{(1)}$ and κ_1 in $mole^{-1}$ l. $sec.^{-1}$ and κ_2 in $mole^{-2}$ $l.^2$ $sec.^{-1}$.]

R	$10^5k_2^{(1)}$ 100°	$10^5k_2^{(1)}$ 60°	$10^5\kappa_1$ 100°	$10^5\kappa_1$ 60°	$10^5\kappa_2$ 100°	$10^5\kappa_2$ 60°	$\kappa_1/k_2^{(1)}$	$a\kappa_2/k_2^{(1)}$	$a\kappa_2/\kappa_1$
Methyl	12·8	0·49	—	35	—	500	71	97	1·26
Neopentyl ...	4·2	—	26·4	—	122	—	6·3	2·7	0·425
Neopentyl / Methyl ...	0·33	—	—	—	—	—	0·089	0·028	0·31

When, having these data for different alkyl groups, we put the alkyl groups under comparison, whilst it is important that rate constants and catalytic constants should be compared only at common temperatures, it is not so important that the dimensionless ratios should, because they do not contain the time dimension. In Table 3 we compare

the methyl and neopentyl groups with respect to their uncatalysed rate-constants at a common temperature for one-alkyl mercury-exchange, and also with respect to the strengths, and relative strengths, of the one-anion and two-anion catalysis of this exchange by bromide ion.

Proceeding now to a discussion of Tables 2 and 3, we can summarise Table 2: the uncatalysed S_E2 rate of one-alkyl mercury-exchange for methyl as the alkyl group, is cut down by factors between 2 and 3 for the ethyl and neopentyl groups, and by a factor of 17 for the s-butyl group. Thus, primary alkyl groups, including neopentyl, can exert only a slight steric effect, whilst the secondary group seems to exert a moderate one.

That this is the kind of pattern of steric effects to be expected from our picture of the configuration-retaining transition state in S_E2 substitutions is shown by the following figures, though they cannot be given more than an illustrative significance, because of the imperfections in our knowledge of the parameters involved.

We first define a " reaction plane," through C_α and the two mercury atoms, and a " median line " on it, through C_α and symmetrically between the mercury atoms. Next we define a " symmetry plane," cutting the reaction plane perpendicularly along the median line. Then the most sterically favourable position for the ethyl group will put C_β on the symmetry plane. The most favourable conformation for the neopentyl group will also put its C_β there, and will place one C_γ in that position, of the possible two in that plane, which is nearer the mercury atoms. The most favourable conformation for the isopropyl group will be such that its secondary hydrogen atom lies in the reaction plane. The s-butyl group can be assumed to have the positions of its C_β atoms similarly determined, its C_γ being then arranged remotely from the mercury atoms. We take the C_α–Hg distance as 2·3 Å (*i.e.*, rather longer than the normal bond length) and the Hg–Hg separation as 3·0 Å (*i.e.*, rather greater than of nearest neighbours in mercury metal). We assume normal dimensions in the alkyl groups. Then it can be computed that, in the ethyl transition-state, the only non-bonding compressions are two equal ones between the β-Me group and the two mercury atoms, each C_β–Hg distance being 3·08 Å. Similarly, in the neopentyl transition state, the only compressions are two equal ones between the symmetrically placed γ-Me group and the two mercury atoms, each C_γ–Hg distance being 3·05 Å. Again, in the isopropyl transition state the only compressions will be two equal ones between the two β-Me groups and one of the mercury atoms, each C_β–Hg distance being 2·70 Å. We suppose that very similar compressions will apply to the β-Me and β-CH_2 groups in the s-butyl transition state.

It is difficult to arrive at a good figure for the methyl–mercury touching distance. But bearing in mind that the only two 6-quantum electrons of mercury are in the bonds, so that it is the core-size that most matters, we have taken the centre-to-centre distance as 3·35 Å. The calculated transition-state compressions are then as follows:

ethyl	2 of 0·27 Å
neopentyl	2 ,, 0·30 Å
isopropyl (s-butyl probably similar)	2 ,, 0·66 Å

Though it is convenient to treat the methyl groups as a whole, the compressions are really with hydrogen atoms, and experience of calculating compression energies between hydrogen and heavy atoms allows us to say at once that the energy resulting from such a calculated compression as 0·3 Å would be of the order of 0·1 kcal./mole, whilst for one of 0·7 Å it would be of the order of 1 kcal./mole. Whilst allowances for entropic effects have to be made, these are clearly the sort of energy figures that could be regarded as consistent with the rate pattern disclosed in Table 2.

The short summary of Table 3 is that, whilst, on changing from methyl to neopentyl as the alkyl group, the S_E2 rate of exchange is cut down by a factor of 3, the S_Ei rates under one-anion and two-anion catalysis are reduced by the respective factors 3×11 and 3×36, *i.e.*, by extra factors of 11 and 36. Evidently the change of mechanism has

brought in extra steric retardation, and more of it into two-anion than into one-anion catalysis.

Qualitatively, these effects should be expected. For whereas in the open S_E2 transition state, all bromine atoms lie in the reaction plane, and hence well out of the way of primary alkyl groups, including the neopentyl group, in the cyclic S_Ei transition states *gem*-Br_2-pairs occur, which are out-of-plane, one such pair in the one-anion transition state, and two in the two-anion (cf. formulæ I and II of Part V [7]); and one bromine atom of each such pair must lie on that side of the reaction plane which contains the bulk of all primary alkyl groups, and in particular, the γ-Me of the neopentyl group. We must obviously expect steric compression between this γ-Me and the nearer bromine atom of each *gem*-Br_2-pair in the S_Ei transition states.

If, for illustration, we take the normal $HgBr_2$ and $HgBr_3^-$ bond-lengths as 2·4 and 2·7 Å, respectively, adopting the latter length for the *gem*-Br_2-pairs, and supposing that the bonds of quadrico-ordinate mercury in the bridged transition states are tetrahedrally arranged, an assumption consistent with reasonable bridge-lengths, then we can calculate that the shortest C_γ–Br distances in the neopentyl one-anion and two-anion transition states are equal to 3·20 Å. There will be one such distance in the one-anion and two in the two-anion transition states. Though the resulting extra compressions in these S_Ei transition states will be between hydrogen and bromine, we may again treat the Me-group as a whole, taking the centre-to-centre CH_3–Br touching distance as 3·95 Å. The extra compressions then become

S_Ei (one-anion catalysis)	1 of 0·75 Å
S_Ei (two-anion catalysis)	2 ,, 0·75 Å

These compressions imply energies in the neighbourhood of 1—2 kcal./mole, which is consistent in order of magnitude with the extra retardations suffered by the S_Ei mechanisms, as compared with the S_E2 mechanism, according to the results in Table 3.

We leave untouched the matter of polar effects of alkyl groups in these reactions. We started by expecting them to be small, because the retention of configuration in all S_E2 mercury exchanges shows that the carbon–metal bond does not become much more ionic in the transition state than it is in the initial state; [3] *i.e.*, there would be little or no polar demand on the alkyl group from the reaction centre. It does seem that polar effects are indeed small enough to be very difficult to distinguish at all in the present results.

Experimental

Materials.—Ethylmercuric bromide was prepared in the usual way from ethylmagnesium bromide and mercuric bromide. Crystallised from ethanol it formed leaflets, m. p. 188—190° (uncorr.) [lit., 198° (corr.)]. Neopentyl chloride, a kind gift from Dr. E. S. Swinbourne, was converted by way of its Grignard derivative in 70% yield, into *neopentylmercuric bromide*,

Table 4. *Run* 149: $[HgBr_2] = 0·0910$, $[neo\text{-}C_5H_{11}HgBr] = 0·0919$, $[LiBr] = 0·188$M. Initially the ^{203}Hg was wholly in the $HgBr_2$. It was measured in timed samples of separated $C_5H_{11}HgBr$. Concentrations and rate-constants are corrected for the thermal volume-change undergone by the solvent, ethanol, on being taken to the reaction temperature, 100·3°.

t (min.)	Count $C_5H_{11}HgBr$ [min.$^{-1}$ (corr.)]	% Reaction $= 100\ (1 - f)$	$10^5 k_{2c}^{(1)}$ (corr.)
0	28·2	3·9	—
20	65·8	12·4	43·0
40	76·8	20·6	44·1
70	152·9	30·0	38·5
105	169·5	40·3	41·4
			41·8

which crystallised from ethanol in needles, m. p. 95—96° (Found: C, 17·1; H, 3·5; Br, 23·4. $C_5H_{11}BrHg$ requires C, 17·1; H, 3·2; Br, 22·7%).

Kinetics.—The methods of starting and stopping runs, of separating products from timed samples for radiometric examination, and the method of examination, were all as described in Part IV [6] for the exchange reaction of methylmercuric bromide with mercuric bromide. The conditions of the runs, and the rate-constants obtained, were as noted in Table 1. A specimen run is recorded in Table 4.

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460. *Cytotoxic Compounds. Part II.*[1] *Some Amides of the "Nitrogen Mustard" Type.*

By M. H. BENN, A. M. CREIGHTON, L. N. OWEN, and G. R. WHITE.

Amides, including urethanes and ureas, have been prepared from *NN*-di-2′-chloroethyl-*p*-phenylenediamine or *p*-(*NN*-di-2-chloroethylamino)phenol. *p*-(*NN*-Di-2-chloroethylamino)phenyl isocyanate is a useful reagent for some of these syntheses. Urethanes and ureas containing the carboxyl group are conveniently made by the use of methyl isocyanatoacetate or *p*-isocyanatobenzoate, followed by mild hydrolysis of the methyl ester; *p*-*NN*-diethylaminophenyl isocyanate can be used to introduce a basic group. An improved synthesis of *p*-(*NN*-di-2-chloroethylamino)phenol is described.

IN continuation of studies [1] on the synthesis of detoxicated "nitrogen mustards" which might become reactivated by enzymic fission at the site of a tumour, some new derivatives of *NN*-di-2′-chloroethyl-*p*-phenylenediamine (I) have been prepared. Carbamates are known [2] to possess cytotoxic properties, but tumours which are initially sensitive to such compounds usually soon become resistant to them. In 1954, Danielli [3] suggested that this was due to the formation of an adaptive enzyme which decomposed the urethane by fission of the ester or peptide linkage. He pointed out that such conditions, once established, should be favourable for the selective activation, at the tumour site, of a "nitrogen mustard" of type (II), in which the highly toxic parent compound (I) has been deactivated by incorporation of the electron-attracting urethane group. Several such compounds (II; Y = Me, Et, Pr^i, Ph, cholesteryl) have therefore been synthesised by one or more of the following methods: (i) reaction of the amine (I) with a chloroformate; (ii) reaction of an alcohol with the isocyanate (VI), either as such or formed *in situ* from the azide (III) or the carbamoyl chloride (IV). The azide was synthesised from the known [4] carboxylic acid *via* the hydrazide, whilst the isocyanate was obtained (though not isolated) by treatment of the amine (I) in toluene with carbonyl chloride. The latter reaction initially gave a solid which showed infrared absorption in the carbonyl region but absence of an isocyanate band; on treatment with water the compound gave two equivalents of hydrogen ion, and was therefore the carbamoyl chloride hydrochloride (IV). When stored under reduced pressure over potassium hydroxide it slowly lost one mol. of hydrogen chloride to form a product which showed only very weak carbonyl but strong isocyanate absorption and was therefore essentially the isocyanate hydrochloride (V); elimination of hydrogen chloride from carbamoyl chlorides is known [5] to occur readily. When the original reaction mixture, containing the solid salt (IV) in

[1] Part I, Benn, Owen, and Creighton, *J.*, 1958, 2800.
[2] Haddow and Sexton, *Nature*, 1946, **157**, 500.
[3] Danielli, Ciba Foundation Symposium, "Leukaemia Research," Churchill, London, 1954, p. 263.
[4] Ross, Warwick, and Roberts, *J.*, 1955, 3110.
[5] Siefken, *Annalen*, 1949, **562**, 75.

suspension, was boiled, hydrogen chloride was evolved and a clear solution of the free isocyanate (VI) was obtained. This compound, its precursors (IV) and (V), and the azide (III) can be used for reactions with various functional groups, and are thus of potential value for the attachment of a nitrogen mustard to a wide variety of other units. The

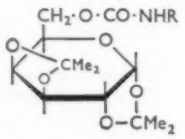
R = p-$(CH_2Cl{\cdot}CH_2)_2N{\cdot}C_6H_4$

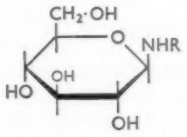
R·NH_2 (I)	R·NH·CO_2Y (II)	R·CON_3 (III)	R·NH·COCl,HCl (IV)	R·NCO,HCl (V)	R·NCO (VI)	R·NH·CO·NHR (VII)

R·NH·CO·NH·C_2H_4·NEt_2 (VIII)	R·NH·CO·NH_2 (IX)	$(CH_2Cl{\cdot}CH_2)_2N{\cdot}CO_2Y$ (X)	R·NH·CO·$[CH_2]_n$·CO_2Y (XI; Y = Et) (XII; Y = H)	$CO_2Me{\cdot}CH_2{\cdot}NCO$ (XIII)

R·NH·CO·NH·CH_2·CO_2Y (XIV; Y = Me) (XV; Y = H)	R·OH (XVI)	R·O·CO·NH·CH_2·CO_2H (XVII)	R·NH·CO·NH·C_6H_4·Y(*p*) (XVIII; Y = CO_2H) (XIX; Y = NEt_2)	R·O·CO·NH·C_6H_4·Y(*p*) (XX; Y = CO_2H) XXI; Y = NEt_2)

(XXII)





(XXIII)

ureas (VII) and (VIII) were prepared by reaction with the amine (I) and *NN*-diethylethylenediamine respectively. The monosubstituted urea (IX) was made from the amine (I) and sodium cyanate. Two of the urethanes (II; Y = Me, Pr^i) were converted into the more reactive bromo-analogues by exchange reactions with lithium bromide.

The aliphatic urethanes (X; Y = Pr^i or cholesteryl) were made from di-(2-chloroethyl)amine and the appropriate chloroformate; the cholesteryl compound was also obtained by displacement of one chloroethyl group from tri-(2-chloroethyl)amine by reaction with cholesteryl chloroformate, a method based on the reported [6] reaction of chloroformates with tertiary amines.

Some of the compounds showed promising results in animal tests,[7] but all were insoluble in water and were usually administered in oily solution or suspension, a method which has disadvantages in clinical practice. It was, therefore, desirable to obtain derivatives containing hydrophilic groups to confer water-solubility.

Reaction of the amine (I) with the ethyl ester chlorides of oxalic, malonic, and succinic acid gave the ester-anilides (XI; $n = 0$, 1, or 2). The ester group in the oxanilate was smoothly removed by brief alkaline hydrolysis, giving the acid (XII; $n = 0$) in good yield. Hydrolysis of the succinanilate was of course much slower, and was probably accompanied by some hydrolysis of the halide groups since only a poor yield of the acid (XII; $n = 2$) could be isolated; better results would probably be obtained with the methyl ester. The acid (XII; $n = 1$) could not be isolated by hydrolysis of the malonate (XI; $n = 1$). Two dianilides were prepared by reaction of the amine (I) with oxalyl and succinyl dichloride.

Methyl isocyanatoacetate (XIII) is a reagent with obvious potentialities for the introduction of a carboxyl group. Prepared from methyl aminoacetate and carbonyl chloride (cf. ref. 5) it reacted with the amine (I) to give the urea (XIV), from which the acid (XV) was obtained by brief hydrolysis with hydrochloric acid; under more vigorous conditions of hydrolysis the corresponding hydantoin was formed. Similarly, the phenolic mustard (XVI) was converted into the urethane (XVII). Methyl *p*-isocyanatobenzoate was also used in the same way, and, although the resulting methyl arylcarboxylates were less readily hydrolysed than the above acetates, the carboxylic acids (XVIII) and

[6] Campbell, *J. Org. Chem.*, 1957, **22**, 1259.
[7] Danielli, *Ann. Reports British Empire Cancer Campaign*, 1957, **35**, 410; 1958, **36**, 527; 1959, **37**, 575.

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(XX) were obtained in good yield. These acids and those described above, though not appreciably water-soluble as such, were soluble in the form of sodium salts.

The introduction of a basic tertiary amino-group, to permit the formation of a hydrochloride or quaternary salt, is another possible method of increasing aqueous solubility. The urea (XIX) and the urethane (XXI) were therefore prepared by reaction of *p*-*NN*-diethylaminophenyl isocyanate with the amine (I) and the phenol (XVI) respectively; the urethane was characterised as the quaternary methiodide, which was readily soluble in water. In contrast to the mustard isocyanate hydrochloride (V), which readily lost hydrogen chloride when heated, the hydrochloride of the much more strongly basic *p*-*NN*-diethylaminophenyl isocyanate could be sublimed; it required heating for 17 hr. in boiling toluene [compared with 10 min. for (V)] for complete conversion into the free isocyanate.

The galactose derivative (XXII) was synthesised (i) by reaction of the mustard isocyanate (VI) with 1,2:3,4-di-*O*-isopropylidene-D-galactose, and (ii) by reaction of the mustard amine (I) with 1,2:3,4-di-*O*-isopropylidene-D-galactose 6-chloroformate. Mild acid-hydrolysis removed both the isopropylidene groups in this urethane to give the 6-substituted galactose, but the hydrophilic properties of the sugar unit were insufficient to endow the product with any marked aqueous solubility. The glucosylamine (XXIII), prepared by reaction of the amine (I) with acetobromoglucose, followed by solvolytic deacetylation, was also only sparingly soluble in water.

The phenolic mustard (XVI) has hitherto been prepared, in very poor yield, by reaction of *p*-(*NN*-di-2-hydroxyethylamino)phenol with phosphorus oxychloride.[4] It seemed likely that side reactions at this stage could be avoided by prior protection of the phenolic group as the benzyl ether, the phenol (XVI) being then obtained by hydrogenolysis of the product, and this procedure has now been found to give much more satisfactory results. It has also now been possible to prepare the phenolic acetate by direct acetylation of the phenol (XVI) under mild conditions, and earlier difficulties[4] were possibly due to the ease with which this ester is hydrolysed back to the phenol. Attempts to make the trichloroacetate were fruitless, for although reaction occurred the ester presumably decomposed when being washed, only the phenol being isolated.

During this work some model compounds were made, containing the phenyl or the *p*-*NN*-diethylaminophenyl group instead of the *p*-(*NN*-di-2-chloroethylamino)phenyl moiety of a mustard. Some of these originated from exploratory experiments, but others were required as substrates for enzymic tests or for investigation as possible biological potentiators. The correctness of Danielli's original hypothesis[3] of adaptive enzyme formation has now been proved,[7] not only with urethanes but also with other compounds; pretreatment of an animal with a suitable model may thus stimulate production of an enzyme capable of hydrolysing the linkage present in the model and hence able also to activate the related nitrogen mustard which is subsequently administered.

The extent of hydrolysis of the halide groups in some of the mustards was determined

Rates of hydrolysis.

R = *p*-(*NN*-Di-2-chloroethylamino)phenyl. R′ = *p*-(*NN*-Di-2-bromoethylamino)phenyl.

Compound	Mmole in acetone (25 c.c.) + water (25 c.c.)	Hydrol. (%) in 30 min. at 66°	Compound	Mmole in acetone (25 c.c.) + water (25 c.c.)	Hydrol. (%) in 30 min at 66°.
R·NH·CO·NH_2	0·4	42	R·NH·CO·CO_2H	0·4	19
R·NH·CO·NH·CH_2·CO_2H	0·3	50	R·NH·CO·$[CH_2]_2$·CO_2H	0·4	28
R·NH·CO_2Me	0·6	33	R·NH·(tetra-*O*-acetyl-glucosyl)	0·4	55
R·NH·CO_2Et	0·5	31	R·O·CO·NHPh	0·5	18
R·NH·CO_2Pr^i	0·5	33	R·O·CH_2Ph	0·3	55
R′·NH·CO_2Me	0·5	88	R′·O·CH_2Ph	0·3	100
R′·NH·CO_2Pr^i	0·5	94			

(Ross's method [8]) by titration of the acid produced after 30 min. in boiling 50% aqueous acetone (see Table); in some cases the amount of halide ion was also measured, and gave a similar result. The urethanes show greater deactivation than the amides, as would be expected from the relative electron-attracting capacities of, *e.g.*, the CO_2Me and the $CO{\cdot}NH_2$ group. The much higher reactivity of the bromo-analogues is apparent.

Experimental

Microanalyses were by Miss J. Cuckney and the staff of the Organic Microanalytical Laboratories.

p-(NN-*Di*-2-*chloroethylamino*)*benzhydrazide*.—*p*-(*NN*-Di-2-chloroethylamino)benzoyl chloride [4] (2·2 g.) in dry ether (50 c.c.) was shaken with pure hydrazine hydrate (7 c.c.) in ethanol (10 c.c.) for 5 min. The granular precipitate was filtered off, combined with the residue obtained by evaporation of the filtrate, and recrystallised from ethanol (charcoal) to give the *hydrazide* as prisms (1·9 g., 88%), m. p. 151° (Found: C, 48·5; H, 5·7; N, 14·5. $C_{11}H_{15}Cl_2N_3O$ requires C, 47·8; H, 5·5; N, 15·2%).

p-(NN-*Di*-2-*chloroethylamino*)*benzazide* (III).—A solution of the above hydrazide (1·6 g.) in concentrated hydrochloric acid (16 c.c.) and water (2 c.c.) was cooled to 0°, and potassium nitrite (0·8 g.) in water (2 c.c.) was added with stirring; a pale yellow solid separated, and after a further 5 min. the mixture was extracted with benzene. Evaporation of the dried extracts gave a solid (1·1 g., 66%), m. p. 110—112°, which when recrystallised from chloroform–light petroleum (b. p. 40—60°) gave the *azide*, yellow prisms, m. p. 114—115° (Found: C, 46·0; H, 4·5; N, 19·3. $C_{11}H_{12}Cl_2N_4O$ requires C, 46·0; H, 4·2; N, 19·5%).

p-(NN-*Di*-2-*chloroethylamino*)*phenylcarbamoyl Chloride Hydrochloride* (IV) (with B. J. Johnson).—*NN*-Di-2′-chloroethyl-*p*-phenylenediamine (from 14 g. of the hydrochloride [9]) in dry toluene (125 c.c.) was slowly added (40 min.) to a stirred solution of liquid carbonyl chloride (50 c.c.) in toluene (125 c.c.), at *ca.* 10°, through which a slow stream of gaseous carbonyl chloride was passed. After a further 45 min., the solid product was collected, washed with dry ether, and freed from solvent under reduced pressure to give the *carbamoyl chloride hydrochloride* (16 g.) as a grey powder (Found, by addition of water and titration with alkali, Cl^-, 21·4. $C_{11}H_{14}Cl_4N_2O$ requires for 2Cl^-, Cl^-, 21·4%), $\nu_{max.}$ (paraffin mull) 1751s, 1715w cm.$^{-1}$.

When the compound was stored at 0·5 mm. over potassium hydroxide, the alkali titre gradually diminished, and after 5 days the product was essentially p-(NN-*di*-2-*chloroethylamino*)*phenyl isocyanate hydrochloride* (V) (Found: Cl^-, 12·1. $C_{11}H_{13}Cl_3N_2O$ requires Cl^-, 12·0%), $\nu_{max.}$ (paraffin mull) 2275s (NCO), *ca.* 1748vw, *ca.* 1709vw cm.$^{-1}$.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl Isocyanate* (VI).—*NN*-Di-2′-chloroethyl-*p*-phenylenediamine (from 10 g. of the hydrochloride) and carbonyl chloride were allowed to react in toluene as described above. The mixture was then boiled under reflux until no more hydrogen chloride was evolved (10 min.), and the resulting homogeneous solution was evaporated under reduced pressure to an oil which contained only a trace of ionic chloride. This could not be purified, but its conversion into urethanes by reaction with alcohols (see below) indicated a content of at least 80% of the isocyanate.

N-p-(NN-*Di*-2-*chloroethylamino*)*phenylcarbamates* (II).—(i) *From* NN-*di*-2′-*chloroethyl*-p-*phenylenediamine*. Methyl chloroformate (0·48 g.) in chloroform (3 c.c.) was added to *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 1·35 g. of hydrochloride) in chloroform (15 c.c.) containing pyridine (0·40 g.). After the exothermic reaction had subsided, the mixture was refluxed for 30 min., cooled, washed with water, dried, and concentrated under reduced pressure to a green oil which crystallised from methanol to give *methyl* N-p-(NN-*di*-2-*chloroethylamino*)-*phenylcarbamate* (1·0 g.), needles, m. p. 99—100° (Found: C, 49·8; H, 5·8; N, 10·1. $C_{12}H_{16}Cl_2N_2O_2$ requires C, 49·5; H, 5·5; N, 9·6%), *ethyl* N-p-(NN-*di*-2-*chloroethylamino*)-*phenylcarbamate*, needles [from ethanol–light petroleum (b. p. 40—60°)], m. p. 80—81° (Found: C, 51·4; H, 6·0; N, 9·05. $C_{13}H_{18}Cl_2N_2O_2$ requires C, 51·2; H, 5·9; N, 9·2%), *isopropyl* N-p-(NN-*di*-2-*chloroethylamino*)*phenylcarbamate*, needles (from methanol), m. p. 87—88° (Found: C, 53·1; H, 6·4; N, 8·8. $C_{14}H_{20}Cl_2N_2O_2$ requires C, 52·8; H, 6·3; N, 8·8%), and *cholesteryl*

[8] Ross, *J.*, 1949, 183.
[9] Everett and Ross, *J.*, 1949, 1972.

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N-p-(NN-*di*-2-*chloroethylamino*)*phenylcarbamate*, a microcrystalline powder (from acetone–methanol), m. p. 68—70°, $[\alpha]_D^{24}$ −16° (*c* 1 in $CHCl_3$) (Found: C, 70·5; H, 9·1; N, 4·2. $C_{36}H_{58}Cl_2N_4O_2$ requires C, 70·7; H, 9·05; N, 4·3%), were prepared similarly in yields of 60—70%.

(ii) *From* p-(NN-*di*-2-*chloroethylamino*)*phenylcarbamoyl chloride hydrochloride*. A solution of the carbamoyl chloride hydrochloride (3 g.) in propan-2-ol (30 c.c.) was heated on the steam-bath for 15 min., then cooled, poured into saturated aqueous sodium hydrogen carbonate (70 c.c.), and extracted with chloroform to give isopropyl *N*-*p*-(*NN*-di-2-chloroethylamino)-phenylcarbamate, which after recrystallisation from methanol had m. p. and mixed m. p. 87—88° (yield, 2·8 g.). The methyl and ethyl esters, identical with those described above, were prepared in the same way. *Phenyl* N-p-(NN-*di*-2-*chloroethylamino*)*phenylcarbamate*, needles (from benzene–ethanol), m. p. 125° (Found: C, 57·5; H, 5·3; N, 7·8. $C_{17}H_{18}Cl_2N_2O_2$ requires C, 57·8; H, 5·1; N, 7·9%), was made by heating equimolecular quantities of the reactants at 100° for 20 min.

Cholesterol (1·0 g.) and the carbamoyl chloride hydrochloride (1·0 g.) in pyridine (30 c.c.) were heated at 100° for 30 min. The cooled solution was poured into water and extracted with chloroform. Removal of solvent under reduced pressure gave a solid residue which was extracted with boiling ethanol; concentration of this extract gave the cholesteryl ester (1·1 g.), m. p. and mixed m. p. 68°. The material insoluble in boiling ethanol was recrystallised from benzene to give needles (0·3 g.) of NN′-*di*-(NN-*di*-2-*chloroethylamino*)*phenylurea* (VII), m. p. 207° (Found: C, 51·2; H, 5·5; N, 11·2. $C_{27}H_{26}Cl_4N_4O$ requires C, 51·2; H, 5·3; N, 11·4%); this was also obtained (4·3 g.) by reaction of the carbamoyl chloride hydrochloride (4 g.) with *NN*-di-2′-chloroethyl-*p*-phenylenediamine hydrochloride (3·8 g.) in pyridine (40 c.c.) for 5 min. at 100°, precipitation of the product by addition of water, and recrystallisation from acetic acid.

(iii) *From* p-(NN-*di*-2-*chloroethylamino*)*phenyl isocyanate*. A solution of the crude isocyanate (0·45 g.) in propan-2-ol (4 c.c.) was refluxed for 15 min., then cooled, poured into water, and extracted with chloroform to give isopropyl *N*-p-(*NN*-di-2-chloroethylamino)phenyl-carbamate (0·4 g.), m. p. and mixed m. p. 88° after recrystallisation from methanol.

(iv) *From* p-(NN-*di*-2-*chloroethylamino*)*benzazide*. A solution of cholesterol (0·6 g.) and the azide (0·5 g.) in petroleum (b. p. 100—120°) (50 c.c.) was boiled under reflux for 3 hr. Removal of solvent and recrystallisation of the residue from ethanol gave cholesteryl *N*-*p*-(*NN*-di-2-chloroethylamino)phenylcarbamate, m. p. 66—68°.

Methyl N-p-(NN-*Di*-2-*bromoethylamino*)*phenylcarbamate*.—A solution of methyl *N*-*p*-(*NN*-di-2-chloroethylamino)phenylcarbamate (1·4 g.) and anhydrous lithium bromide (5 g.) in isobutyl methyl ketone (25 c.c.) was boiled under reflux for 5 hr., then cooled and poured into water. Extraction with ether gave the *dibromo-compound* (0·95 g.), needles [from chloroform–light petroleum (b. p. 60—80°)], m. p. 113° (Found: Br, 41·7; N, 7·6. $C_{12}H_{16}Br_2N_2O_2$ requires Br, 42·0; N, 7·4%).

Isopropyl N-p-(NN-*Di*-2-*bromoethylamino*)*phenylcarbamate*.—Prepared similarly, this *compound* crystallised from chloroform–light petroleum (b. p. 60—80°) in plates, m. p. 90—91° (Found: Br, 39·2; N, 6·95. $C_{14}H_{20}Br_2N_2O_2$ requires Br, 39·2; N, 6·9%).

Isopropyl Di-2-*chloroethylcarbamate* (X; Y = Pr^i).—Isopropyl chloroformate (10·3 g.) was added dropwise to di-(2-chloroethyl)amine (from 14·5 g. of hydrochloride) and pyridine (8 c.c.) in chloroform (150 c.c.). The mixture was then refluxed for 15 min., cooled, washed with water, dried, and distilled to give the *urethane* (15·1 g., 81%), b. p. 102—104°/2 mm., n_D^{21} 1·4634 (Found: C, 42·5; H, 6·9; Cl, 31·2. $C_8H_{15}Cl_2NO_2$ requires C, 42·1; H, 6·6; Cl, 31·1%).

Cholesteryl Di-2-*chloroethylcarbamate* (X; Y = *cholesteryl*).—(i) Similar reaction of cholesteryl chloroformate[10] (2·3 g.) with di-(2-chloroethyl)amine (from 1·9 g. of hydrochloride) in chloroform (70 c.c.) gave, after removal of solvent, a solid which was recrystallised from acetone–methanol to give the *urethane* as needles (2·25 g., 79%), m. p. 111—112°, $[\alpha]_D^{22}$ −18° (*c* 1 in $CHCl_3$) (Found: C, 69·0; H, 9·9; Cl, 13·1. $C_{32}H_{53}Cl_2NO_2$ requires C, 69·3; H, 9·6; Cl, 12·8%).

(ii) A solution of cholesteryl chloroformate (0·45 g.) and tri-(2-chloroethyl)amine (from 4 g. of hydrochloride) in benzene (45 c.c.) was refluxed for 2 hr., then cooled, washed successively with water, 2N-hydrochloric acid, and water, dried, and concentrated to an oil. Purification by

[10] Wieland, Honold, and Pascual-Vila, *Z. physiol. Chem.*, 1923, **130**, 326.

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chromatography in benzene on alumina, followed by recrystallisation from acetone–methanol, gave the same urethane, m. p. and mixed m. p. 110°.

Di-p-(NN-*di*-2-*chloroethylamino*)*anilides of Dibasic Acids*.—A solution of *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 5·4 g. of hydrochloride) and triethylamine (2·0 g.) in chloroform (75 c.c.) was treated dropwise with oxalyl dichloride (1·3 g.) in ether (10 c.c.). The mixture was refluxed for 15 min., cooled, washed with water, dried, and concentrated to an oil, which crystallised from chloroform–ethanol to give pp′-*di*-(NN-*di*-2-*chloroethylamino*)*oxanilide*, needles (2·6 g.), m. p. 156—157° with a second m. p. 170—171° (Found: C, 50·9; H, 5·0; N, 10·7. $C_{22}H_{26}Cl_4N_4O_2$ requires C, 50·8; H, 5·0; N, 10·8%). The *derivative* of succinic acid, prepared similarly, formed needles (from chloroform–ethanol), m. p. 169° (Found: C, 52·3; H, 5·7; N, 10·2. $C_{24}H_{30}Cl_4N_4O_2$ requires C, 52·6; H, 5·5; N, 10·2%).

Ethyl Esters of p-(NN-*Di*-2-*chloroethylamino*)*anilic Acids* (XI).—Addition of ethyl succinyl chloride (1·85 g.) in chloroform (10 c.c.) to *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 3 g. of hydrochloride) in chloroform (50 c.c.) containing triethylamine (1·1 g.) gave *ethyl* p-(NN-*di*-2-*chloroethylamino*)*succinanilate*, which crystallised from ethanol–light petroleum (b. p. 40—60°) in needles (2·9 g.), m. p. 111—112° (Found: C. 53·5; H, 6·6; N, 7·8. $C_{16}H_{22}Cl_2N_2O_3$ requires C, 53·2; H, 6·1; N, 7·8%). The *derivative* of malonic acid, needles (from ethanol), m. p. 87° (Found: C, 51·7; H, 5·8; N, 8·4. $C_{15}H_{20}Cl_2N_2O_3$ requires C, 51·9; H, 5·8; N, 8·1%), and the *derivative* of oxalic acid, pale yellow needles (from ethanol), m. p. 138—139° (Found: C, 50·8; H, 5·7; Cl, 21·0. $C_{14}H_{18}Cl_2N_2O_3$ requires C, 50·5; H, 5·45; Cl, 21·3%), were prepared similarly.

p-(NN-*Di*-2-*chloroethylamino*)*anilic Acids* (XII).—(i) N-Ethanolic potassium hydroxide (3 c.c.) was added to ethyl *p*-(*NN*-di-2-chloroethylamino)oxanilate (1·0 g.) in hot ethanol (30 c.c.), and the solution was heated under reflux for 5 min., concentrated to about 10 c.c., and diluted with ether (50 c.c.). The precipitated salt (0·9 g.) was collected, dissolved in water (30 c.c.), acidified with a slight excess of dilute hydrochloric acid, and extracted with ether to give a solid, which on recrystallisation from ethanol–light petroleum (b. p. 60—80°) gave p-(NN-*di*-2-*chloroethylamino*)*oxanilic acid*, yellow prisms (0·8 g., 88%), m. p. 149° (Found: C, 47·5; H, 4·8; Cl, 23·3. $C_{12}H_{14}Cl_2N_2O_3$ requires C, 47·2; H, 4·6; Cl, 23·2%).

(ii) N-Ethanolic potassium hydroxide (5·5 c.c.) was added slowly (20 min.) to ethyl *p*-(*NN*-di-2-chloroethylamino)succinanilate (2·0 g.) in boiling ethanol (30 c.c.). The solution, which was then neutral, was evaporated to dryness, and the solid residue was washed with chloroform, then dissolved in water (40 c.c.), treated with a slight excess of 2N-hydrochloric acid, and extracted with chloroform to give an oil which partly crystallised. The solid was collected and extracted with boiling ether; evaporation of this extract gave p-(NN-*di*-2-*chloroethylamino*)-*succinanilic acid* (0·2 g.), which after recrystallisation from acetone–ether had m. p. 118—120° (Found: C, 50·2; H, 5·7; N, 8·4. $C_{14}H_{18}Cl_2N_2O_3$ requires C, 50·5; H, 5·5; N, 8·4%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-N′-(2-NN-*diethylaminoethyl*)*urea* (VIII).—A solution of *NN*-diethylethylenediamine (1·1 g.) and *p*-(*NN*-di-2-chloroethylamino)phenyl isocyanate (2·6 g.) in dry ether (10 c.c.) was heated under reflux for 3 hr. Evaporation then gave the crude urea (2·8 g.) as an oil. It formed a *picrate*, m. p. 138° (from ethanol) (Found: C, 45·6; H, 5·5; Cl, 11·6. $C_{23}H_{31}Cl_2N_7O_8$ requires C, 45·7; H, 5·2; Cl, 11·7%).

p-(NN-*Di*-2-*chloroethylamino*)*phenylurea* (IX).—To *NN*-di-2′-chloroethyl-*p*-phenylenediamine hydrochloride (6·4 g.) in acetic acid (100 c.c.), a solution of sodium cyanate (1·6 g.) in water (3 c.c.) was added. The mixture was heated on a steam-bath for 10 min., then allowed to cool and poured into water (600 c.c.). The precipitated solid, recrystallised from ethanol, gave the *urea* as needles (4·5 g., 69%), m. p. 140—141° (Found: C, 48·6; H, 5·7; N, 15·3. $C_{11}H_{13}Cl_2N_3O$ requires C, 48·8; H, 5·5; N, 15·2%).

Methyl Isocyanatoacetate.—A solution of carbonyl chloride (110 g.) in toluene (270 c.c.) was added at 25° to a stirred suspension of methyl aminoacetate hydrochloride (68·5 g.) in toluene (210 c.c.), and the mixture was then stirred and refluxed in a stream of carbonyl chloride for 7 hr. After being cooled, it was filtered and concentrated to an oil which on distillation gave *methyl isocyanatoacetate* (37·3 g., 59%), b. p. 73°/19 mm., n_D^{21} 1·4286 (Found: C, 41·3; H, 4·4; N, 11·9. $C_4H_5NO_3$ requires C, 41·7; H, 4·4; N, 12·2%).

Ethyl p-(NN-*Di*-2-*chloroethylamino*)*phenylureidoacetate*.—*NN*-Di-2′-chloroethyl-*p*-phenylenediamine (from 5·4 g. of the hydrochloride) in ether (120 c.c.) was added to ethyl isocyanatoacetate [5] (2·6 g.) in ether (10 c.c.), and the mixture, in which a white precipitate was formed, was refluxed for 20 min. and then cooled. The solid, on recrystallisation from methanol, gave

the *ureidoacetate* (6·5 g., 90%), m. p. 130° (Found: C, 50·2; H, 5·9; Cl, 20·0. $C_{15}H_{21}Cl_2N_3O_3$ requires C, 49·7; H, 5·8; Cl, 19·6%).

Methyl p-(NN-*Di*-2-*chloroethylamino*)*phenylureidoacetate* (XIV).—Similar reaction of *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 10 g. of hydrochloride) and methyl isocyanatoacetate (4·5 g.) gave, on recrystallisation from methanol, the *ureidoacetate* (10·0 g., 77%), m. p. 124° (Found: Cl, 19·4. $C_{14}H_{19}Cl_2N_3O_3$ requires Cl, 20·3%).

p-(NN-*Di*-2-*chloroethylamino*)*phenylureidoacetic Acid* (XV).—(i) A suspension of ethyl *p*-(*NN*-di-2-chloroethylamino)phenylureidoacetate (3·1 g.) in N-hydrochloric acid (85 c.c.) was refluxed for 12 min. to give a homogeneous solution. The cooled (0°) reaction mixture was partly neutralised (to pH 4) with 2N-sodium hydroxide, and the solid was collected and crystallised from ethanol–light petroleum (b. p. 40—60°) to give the *acid* as the *monoethanolate* (1·6 g., 56%), m. p. 81—82° (Found: C, 46·6; H, 5·8; Cl, 18·5%; equiv., 380. $C_{13}H_{17}Cl_2N_3O_3$,EtOH requires C, 47·4; H, 6·1; Cl, 18·65%; equiv., 380).

(ii) The methyl ester (10 g.) was hydrolysed in 3 min. in boiling N-hydrochloric acid (140 c.c.) to give the acid, which after recrystallisation as above gave the same ethanolate (6·7 g., 61%), m. p. 81—82°.

3-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]*hydantoin*.—A solution of ethyl *p*-(*NN*-di-2-chloroethylamino)phenylureidoacetate (0·7 g.) in acetic acid–concentrated hydrochloric acid (1 : 1; 5 c.c.) was boiled for 3 min. and then cooled to 0°. Ice-water (5 c.c.) was added and the precipitate was collected, dried, and recrystallised from benzene to give the *hydantoin* (0·4 g.), m. p. 180° (Found: C, 49·9; H, 4·65; Cl, 22·1. $C_{13}H_{15}Cl_2N_3O_2$ requires C, 49·4; H, 4·8; Cl, 22·4%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Methoxycarbonylmethyl*)*carbamate*.—*p*-(*NN*-Di-2-chloroethylamino)phenol (from 9·6 g. of hydrochloride) and methyl isocyanatoacetate (4·1 g.) were heated together at 100—110° for 15 hr. in a sealed tube and then cooled. The oil crystallised on trituration with ether, and recrystallisation from carbon tetrachloride–light petroleum (b. p. 40—60°) gave the *urethane* (6·5 g., 45%), m. p. 102° (Found: Cl, 20·2; N, 8·0. $C_{14}H_{18}Cl_2N_2O_4$ requires Cl, 20·3; N, 8·0%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Carboxymethyl*)*carbamate* (XVII).—A solution of *p*-(*NN*-di-2-chloroethylamino)phenyl *N*-(methoxycarbonylmethyl)carbamate (4·0 g.) in acetic acid–concentrated hydrochloric acid (1 : 1; 25 c.c.) was boiled for 3 min., then cooled, diluted with water, and brought to pH 4 with 2N-sodium hydroxide. Extraction with chloroform gave the acid as an oil, which was characterised as the S-*benzylthiouronium salt*, m. p. 143° (from nitromethane) (Found: C, 50·8; H, 5·4. $C_{21}H_{26}Cl_2N_4O_4S$ requires C, 50·3; H, 5·2%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-N′-[p-(*methoxycarbonyl*)*phenyl*]*urea*.—Methyl *p*-isocyanatobenzoate [5] (3·5 g.) in dry ether (50 c.c.) was added to *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 5·3 g. of hydrochloride) in ether (85 c.c.). The mixture was refluxed for 30 min., then cooled, and the white precipitate was recrystallised from methanol to give needles of the *urea* (7·5 g., 92%), m. p. 179—180° (Found: C, 55·8; H, 5·3; Cl, 17·1. $C_{19}H_{21}Cl_2N_3O_3$ requires C, 55·6; H, 5·2; Cl, 17·3%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-N′-(p-*carboxyphenyl*)*urea* (XVIII).—The above methyl ester (0·4 g.) was boiled with acetic acid–concentrated hydrochloric acid (1 : 1; 5 c.c.) under reflux for 35 min., then cooled and diluted with water (10 c.c.). The precipitated product could not be satisfactorily recrystallised; after precipitation from ethanol with light petroleum (b. p. 40—60°) the acid (0·3 g.) had m. p. >300° (decomp.). It gave an S-*benzylthiouronium salt*, m. p. 163° (from acetonitrile) (Found: C, 55·0; H, 5·3; Cl, 12·4. $C_{26}H_{29}Cl_2N_5O_3S$ requires C, 55·5; H, 5·2; Cl, 12·6%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-*Methoxycarbonylphenyl*)*carbamate*.—A mixture of *p*-(*NN*-di-2-chloroethylamino)phenol (4·7 g.), methyl *p*-isocyanatobenzoate (3·55 g.), and pyridine (0·1 g.) was heated at 100° for 2 hr. in a sealed tube. Recrystallisation of the solid product from nitromethane gave the *urethane* (5·0 g., 61%), m. p. 164° (Found: C, 55·3; H, 4·8; Cl, 17·0. $C_{19}H_{20}Cl_2N_2O_4$ requires C, 55·5; H, 4·9; Cl, 17·2%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-*Carboxyphenyl*)*carbamate* (XX).—Hydrolysis of the above methyl ester (4·4 g.), as described for the corresponding urea, gave the *acid*, which was purified by precipitation from ethyl acetate with light petroleum (b. p. 40—60°), then forming a white powder (4·0 g., 94%), m. p. 207° (Found: C, 54·5; H, 4·9; Cl, 18·0. $C_{18}H_{18}Cl_2N_2O_4$ requires C, 54·4; H, 4·6; Cl, 17·85%).

p-NN-*Diethylaminophenyl Isocyanate*.—*p*-*NN*-Diethylaminoaniline (from 50 g. of hydrochloride) in toluene (200 c.c.) was added to a stirred solution of carbonyl chloride (79 g.) in

toluene (200 c.c.), a stream of carbonyl chloride being passed through and maintained whilst the stirred mixture was refluxed for 2 hr. A portion of the supernatant solution was decanted from the oil and cooled to deposit needles, which on recrystallisation from benzene–light petroleum (b. p. 40—60°) followed by vacuum-sublimation at 130—160°/10^{-4} mm. gave p-NN-*diethylaminophenyl isocyanate hydrochloride*, m. p. 133—135°, $\nu_{max.}$ (paraffin mull) 2269 and 2381 $cm.^{-1}$ (NCO) (Found: C, 58·0; H, 6·7; N, 12·0. $C_{11}H_{15}ClN_2O$ requires C, 58·3; H, 6·6; N, 12·4%).

The main bulk of the reaction mixture was refluxed in a slow stream of nitrogen for 17 hr.; a homogeneous solution resulted. This was concentrated under reduced pressure to an oil which on distillation gave p-NN-*diethylaminophenyl isocyanate* (23·5 g., 49%), b. p. 104°/10^{-2} mm., n_D^{22} 1·5692 (Found: C, 69·6; H, 7·8; N, 14·2. $C_{11}H_{14}N_2O$ requires C, 69·4; H, 7·4; N, 14·7%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-N′-(p-NN-*diethylaminophenyl*)*urea* (XIX).—*p*-*NN*-Diethylaminophenyl isocyanate (0·9 g.) in ether (5 c.c.) was added to *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 1·35 g. of hydrochloride) in ether (45 c.c.). After 30 min. the precipitate was filtered off and recrystallised from methanol to give needles of the *urea* (1·7 g., 68%), m. p. 165° (Found: C, 60·1; H, 6·9; Cl, 17·0. $C_{21}H_{28}Cl_2N_4O$ requires C, 59·6; H, 6·7; Cl, 16·75%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-NN-*Diethylaminophenyl*)*carbamate* (XXI).—*p*-(*NN*-Di-2-chloroethylamino)phenol (from 5·4 g. of hydrochloride) and *p*-*NN*-diethylaminophenyl isocyanate (3·7 g.) were heated together at 125° for 26 hr. in a sealed tube and then cooled. The oil solidified when shaken with ether to give the urethane (4·7 g., 56%), m. p. 95—105°, which could not be satisfactorily recrystallised. On reaction for 24 hr. with boiling methyl iodide it gave the *methiodide*, m. p. 168—170° (from methanol–ether) (Found: C, 47·1; H, 5·6. $C_{22}H_{30}Cl_2IN_3O_2$ requires C, 46·65; H, 5·3%).

1,2:3,4-*Di*-O-*isopropylidene*-D-*galactose* 6-{N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]*carbamate*} (XXII).—(i) 1,2:3,4-Di-*O*-isopropylidene-D-galactose 6-chloroformate [11] (6·0 g.) in chloroform (30 c.c.) was added to a solution of *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 5 g. of hydrochloride) and pyridine (3 c.c.) in chloroform (120 c.c.). The solution was set aside for 30 min., then washed with water, dried, and concentrated to an oil, which was purified by chromatography in benzene on alumina. Evaporation of the earlier fractions of the eluate left a glass, which crystallised from pentane to give the slightly impure *urethane* (0·6 g.), m. p. 58°, $[\alpha]_D^{23}$ −41° (*c* 4 in $CHCl_3$) (Found: C, 52·2; H, 6·4; Cl, 13·65. $C_{23}H_{32}Cl_2N_2O_7$ requires C, 53·2; H, 6·2; Cl, 12·9%).

(ii) *p*-(*NN*-Di-2-chloroethylamino)phenyl isocyanate (4·4 g.) and 1,2:3,4-di-*O*-isopropylidene-D-galactose [12] (4·4 g.) were heated in a sealed tube at 100° for 15 hr. The oil was purified by chromatography, as described above, and after recrystallisation from pentane gave, in very poor yield, the same carbamate, m. p. 58—59°.

D-*Galactose* 6-{N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]*carbamate*}.—The above di-*O*-isopropylidene compound (0·20 g.) in acetic acid (10·0 c.c.) showed (1 dm. tube) α_D^{24} −0·57°. After addition of concentrated hydrochloric acid (10·0 c.c.) this became α_D^{24} +0·32°, unchanged after 1 hr. Evaporation under reduced pressure below 45° gave a glass which was purified by precipitation from methanol with ether to give the amorphous *carbamate* (0·12 g.) (Found: C, 45·9; H, 5·3; Cl, 17·1. $C_{17}H_{24}Cl_2N_2O_7$ requires C, 46·5; H, 5·5; Cl, 16·1%). It was only sparingly soluble in water.

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucosylamine*.—A solution of α-acetobromoglucose (26 g.) in chloroform (150 c.c.) containing *NN*-di-2′-chloroethyl-*p*-phenylenediamine (from 17 g. of hydrochloride) was left at room temperature overnight, then washed with water, dried, and concentrated to a syrup which crystallised on trituration with ethanol–light petroleum (b. p. 40—60°). Recrystallisation from ethanol gave the *tetra*-O-*acetyl*-β-D-*glucosyl derivative* as needles (12 g., 68%), m. p. 158—159°, $[\alpha]_D^{19}$ −17° (*c* 2 in $CHCl_3$) (Found: C, 51·3; H, 5·9. $C_{24}H_{32}Cl_2N_2O_9$ requires C, 51·1; H, 5·7%).

N-[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-β-D-*glucosylamine* (XXIII).—The tetra-acetyl compound (2·0 g.) was suspended in dry methanol (30 c.c.) and a trace of sodium (*ca.* 5 mg.) was added. The mixture was shaken until homogeneous, stored overnight at 0°, then saturated with carbon dioxide and evaporated to dryness. The residue was taken up in hot ethanol

[11] Haworth, Porter, and Waine, *Rec. Trav. chim.*, 1938, **57**, 541.
[12] Raymond and Schroeder, *J. Amer. Chem. Soc.*, 1948, **70**, 2785.

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(50 c.c.), filtered, and again evaporated to yield the *glucosylamine* as a glass (1·25 g., 89%) (Found: C, 48·3; H, 6·3. $C_{14}H_{24}Cl_2N_2O_5$ requires C, 48·6; H, 6·1%).

Benzyl p-(NN-*Di*-2-*hydroxyethylamino*)*phenyl Ether*.—*p*-(*NN*-Di-2-hydroxyethylamino)-phenol [4] (50·0 g.), potassium hydroxide (14·2 g.), benzyl bromide (43·4 g.), and ethanol (350 c.c.) were heated together under reflux for 2 hr., then concentrated and poured into water. The precipitate (61·5 g., 85%), m. p. 86—89°, on recrystallisation from ethanol–light petroleum (b. p. 60—80°) gave the *ether* as needles, m. p. 93—94° (Found: C, 70·8; H, 7·5. $C_{17}H_{21}NO_3$ requires C, 71·0; H, 7·4%).

Benzyl p-(NN-*Di*-2-*chloroethylamino*)*phenyl Ether*.—The above dihydroxy-ether (3·0 g.) in chloroform (20 c.c.) was treated with phosphorus pentachloride (4·9 g.). When the vigorous reaction had subsided, the solution was heated under reflux for 90 min. and then cooled and poured into water. The chloroform layer was separated, washed with aqueous sodium carbonate, dried, and concentrated to an oil, which was passed in benzene through a column of alumina. Concentration of the eluates gave colourless plates of *benzyl* p-(NN-*di*-2-*chloroethylamino*)*phenyl ether* (2·4 g., 70%), m. p. 72—73° [from ethanol–light petroleum (b. p. 60—80°)] (Found: C, 63·0; H, 6·05; Cl, 22·1. $C_{17}H_{19}Cl_2NO$ requires C, 63·0; H, 5·9; Cl, 21·9%). Subsequent preparations had m. p. 105—106°, undepressed on admixture with the lower-melting variety. After being set aside for a few weeks, however, the original sample also melted at 105—106°.

p-(NN-*Di*-2-*chloroethylamino*)*phenol Hydrochloride*.—A suspension of the above dichloro-ether (23 g.) in methanol (250 c.c.) was saturated with hydrogen chloride until complete dissolution occurred, then concentrated until solid began to separate. Addition of ether gave prisms of the hydrochloride (22 g.), m. p. 135—136°. On storage, it lost hydrogen chloride and reverted to the free base after 2 days.

The freshly prepared hydrochloride (20·0 g.) was suspended in ethanol (200 c.c.) containing 2½% palladised charcoal (1·0 g.) and hydrogenated for 7 hr. at atmospheric pressure to give, after filtration and concentration, *p*-(*NN*-di-2-chloroethylamino)phenol hydrochloride (14 g., 93%), m. p. 170—173° (lit.,[4] m. p. 168°). The free base, liberated from the hydrochloride, reacted with phenyl isocyanate at 100° for 2 hr. to give p-(NN-*di*-2-*chloroethylamino*)*phenyl* N-*phenylcarbamate*, m. p. 136° (from benzene–ethanol) (Found: C, 58·0; H, 5·3; N, 7·8; Cl, 19·9. $C_{17}H_{18}Cl_2N_2O_2$ requires C, 57·8; H, 5·1; N, 7·9; Cl, 20·1%).

Benzyl p-(NN-*Di*-2-*bromoethylamino*)*phenyl Ether*.—Prepared from the dichloro-analogue (4·0 g.) and lithium bromide (5 g.) in boiling isobutyl methyl ketone for 6 hr., the *dibromide* formed rhombs, m. p. 106° [from chloroform–light petroleum (b. p. 60—80°)] (Found: Br, 38·9. $C_{17}H_{19}Br_2NO$ requires Br, 38·7%).

p-(NN-*Di*-2-*hydroxyethylamino*)*phenyl* 4-*Nitrobenzyl Ether*.—Prepared from *p*-(*NN*-di-2-hydroxyethylamino)phenol and 4-nitrobenzyl bromide in the same way as described above for the benzyl ether, the *4-nitrobenzyl ether* formed orange needles, m. p. 125—126° (from ethanol) (Found: C, 61·4; H, 6·2. $C_{17}H_{20}N_2O_5$ requires C, 61·4; H, 6·1%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* 4-*Nitrobenzyl Ether*.—Reaction of the above diol with phosphorus pentachloride in chloroform gave the *dichloro-ether* as yellow needles, m. p. 73° (from ethanol) (Found: C, 55·3; H, 5·0; Cl, 19·2. $C_{17}H_{18}Cl_2N_2O_3$ requires C, 55·3; H, 4·9; Cl, 19·2%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl Acetate*.—*p*-(*NN*-Di-2-chloroethylamino)phenol hydrochloride (2·7 g.) in pyridine (20 c.c.) was added during 5 min. to acetyl chloride (0·7 c.c.) in pyridine (5 c.c.) at −8°. The mixture was kept for a further 5 min. at −8°, then diluted with ice-water (15 c.c.) and extracted with chloroform (3 × 10 c.c.). The extracts were quickly washed with dilute hydrochloric acid at 0°, then dried and evaporated to give the acetyl derivative as an oil (2·2 g., 80%), $\nu_{max.}$ (liquid film) 1757 (C=O in phenyl acetate), 1209 cm.$^{-1}$ (C–O in phenyl acetate) (Found: Cl, 25·1. Calc. for $C_{12}H_{15}Cl_2NO_2$: Cl, 25·7%).

ω-*Fluoroacetanilide*.—Prepared by reaction of aniline with fluoroacetyl chloride in ether, the *compound* crystallised from aqueous ethanol in flakes, m. p. 74—75° (Found: C, 62·4; H, 5·4; N, 9·4. C_8H_8FNO requires C, 62·8; H, 5·3; N, 9·15%).

p-NN-*Diethylaminobenzoic Acid*.—*p*-Bromo-*NN*-diethylaniline (56 g.) in dry tetrahydrofuran (200 c.c.) was added dropwise (30 min.) to magnesium turnings (6 g.), a trace of iodine, and dry tetrahydrofuran (50 c.c.). The mixture was refluxed for 30 min. (during which almost all the magnesium dissolved), then cooled and transferred to an autoclave containing crushed solid carbon dioxide (*ca.* 500 g.). The autoclave was sealed, warmed to 50° for 2 hr., and allowed to cool overnight, stirring being maintained throughout. The mixture was then

treated with saturated ammonium chloride solution (250 c.c.) and made alkaline with ammonia. It was extracted with ether (2 × 100 c.c.) (the extracts being rejected), and the aqueous solution adjusted to pH 6 with 6N-hydrochloric acid. The precipitated acid was taken up in ether (4 × 100 c.c.), in which it is rather sparingly soluble, and this solution was dried and evaporated to a residue which on recrystallisation from ethanol gave *p-NN*-diethylaminobenzoic acid, m. p. 193° (lit.,[13] m. p. 193°). A further quantity of acid was obtained from the aqueous mother-liquors by concentration. The total yield was 17 g. (38%). The S-*benzylthiouronium salt* crystallised from ethanol in needles, m. p. 187—188° (Found: C, 63·2; H, 7·2. $C_{19}H_{25}N_3O_3S$ requires C, 63·5; H, 7·0%).

Methyl p-NN-*Diethylaminobenzoate*.—Prepared in quantitative yield by reaction of the acid with ethereal diazomethane, this *methyl ester* formed prisms (from methanol), m. p. 46—47° (Found: C, 69·4; H, 8·4. $C_{12}H_{17}NO_2$ requires C, 69·5; H, 8·3%).

p-NN-*Diethylaminobenzhydrazide*.—A mixture of methyl *p-NN*-diethylaminobenzoate (14 g.) and 90% hydrazine hydrate (10 c.c.) was refluxed for 18 hr. Evaporation under reduced pressure gave the hydrazide as a glass which was characterised by condensation with benzaldehyde, to give the *benzylidene derivative*, pale yellow needles (from ethanol), m. p. 218° (Found: C, 73·2; H, 7·5. $C_{18}H_{21}NO_2$ requires C, 73·2; H, 7·2%).

p-NN-*Diethylaminobenzazide*.—A solution of the crude hydrazide (6·0 g.) in 3N-hydrochloric acid (100 c.c.) was cooled to 0° and potassium nitrite (4·8 g.) in water (20 c.c.) was added dropwise with stirring and cooling. The solution was kept at 0° for 10 min., then poured into saturated aqueous sodium acetate solution at 0°, and the precipitated *azide* was collected, dried, and recrystallised from light petroleum (b. p. 40—60°) as pale yellow needles (4·2 g., 67%), m. p. 50° (Found: C, 60·7; H, 6·4. $C_{11}H_{14}N_4O$ requires C, 60·5; H, 6·5%).

Urethanes derived from p-NN-*Diethylaminobenzazide*.—(i) A solution of the azide (0·2 g.) and phenol (0·1 g.) in dry benzene (5 c.c.), when refluxed for 4 hr. and then evaporated, gave *phenyl* N-(p-NN-*diethylaminophenyl*)*carbamate*, needles (from methanol), m. p. 125—126° (Found: C, 71·5; H, 7·2. $C_{17}H_{20}N_2O_2$ requires C, 71·8; H, 7·1%).

(ii) *Cholesteryl* N-(p-NN-*diethylaminophenyl*)*carbamate*, prepared similarly, crystallised from ethanol in needles, m. p. 133°, $[\alpha]_D^{20}$ −19·6° (*c* 1·6 in $CHCl_3$) (Found: C, 79·1; H, 10·5. $C_{36}H_{60}N_2O_2$ requires C, 79·1; H, 10·5%).

N-(p-NN-*Diethylaminophenyl*)-N′-*phenylurea*, prepared by heating *p-NN*-diethylaminobenzazide with aniline in dry benzene, formed needles, m. p. 182—183° (from ethanol) (Found: C, 72·0; H, 7·5. $C_{17}H_{21}N_3O$ requires C, 72·05; H, 7·5%).

Isopropyl N-(p-NN-*Diethylaminophenyl*)*carbamate*.—Isopropyl chloroformate was treated with *p-NN*-diethylaminoaniline as described above for the reaction with *NN*-di-2′-chloroethyl-*p*-phenylenediamine. Distillation of the product gave the *urethane*, b. p. 148—150°/10^{-4} mm. (Found: C, 67·0; H, 8·7; N, 11·3. $C_{14}H_{22}N_2O_2$ requires C, 67·2; H, 8·9; N, 11·2%).

N-(p-NN-*Diethylaminophenyl*)-2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucosylamine*.—α-Acetobromoglucose was treated with *p-NN*-diethylaminoaniline, as described above for the reaction with *NN*-di-2′-chloroethyl-*p*-phenylenediamine, to give the *tetra*-O-*acetylglucosylamine*, needles (from ethanol), m. p. 135°, $[\alpha]_D^{20}$ −31° (*c* 2 in $CHCl_3$) (Found: C, 58·4; H, 7·1; N, 5·7. $C_{24}H_{34}N_2O_9$ requires C, 58·3; H, 6·9; N, 5·7%).

N-(2-NN-*Diethylaminoethyl*)-N′-*phenylurea*.—Reaction of *NN*-diethylethylenediamine with phenyl isocyanate gave the *urea*, b. p. 171°/10^{-2} mm. (Found: C, 66·5; H, 9·15; N, 17·5. $C_{13}H_{21}N_3O$ requires C, 66·3; H, 9·0; N, 17·9%). When triturated with concentrated hydrochloric acid it was rapidly converted into diphenylurea, m. p. 243°.

p-NN-*Diethylaminoacetanilide*, prepared by acetylation of the free base with acetic anhydride, had m. p. 104° after recrystallisation from aqueous ethanol (Found: C, 69·7; H, 8·8. $C_{12}H_{18}N_2O$ requires C, 69·9; H, 8·8%).

N-(p-NN-*Diethylaminophenyl*)-N′-p-*hydroxyphenylurea*.—Reaction of equimolecular proportions of *p*-aminophenol and *p-NN*-diethylaminophenyl isocyanate in boiling tetrahydrofuran gave the *urea*, m. p. 185° (from aqueous methanol) (Found: C, 68·1; H, 7·0; N, 13·85. $C_{17}H_{21}N_3O_2$ requires C, 68·2; H, 7·1; N, 14·0%).

N-p-*Aminophenyl*-N′-(p-NN-*diethylaminophenyl*)*urea*.—Similar reaction of equimolecular proportions of *p*-phenylenediamine and *p-NN*-diethylaminophenyl isocyanate gave the *urea*, m. p. 174—175° (from benzene) (Found: C, 68·7; H, 7·3; N, 18·45. $C_{17}H_{22}N_4O$ requires C, 68·4; H, 7·4; N, 18·8%).

[13] Kumler, *J. Amer. Chem. Soc.*, 1946, **68**, 1184.

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1,2:3,4-*Di*-O-*isopropylidene*-D-*galactose* 6-[N-(p-NN-*Diethylaminophenyl*)*carbamate*].—*p-NN*-Diethylaminophenyl isocyanate (4·3 g.) and 1,2:3,4-di-*O*-isopropylidene-D-galactose (6·0 g.) were heated together in a sealed tube at 100° for 20 hr. Recrystallisation of the product from light petroleum (b. p. 30—40°) at −30° gave the *carbamate* as a low-melting solid, which became a glass at room temperature (Found: C, 60·7; H, 7·6; N, 6·4. $C_{23}H_{34}N_2O_7$ requires C, 61·3; H, 7·6; N, 6·2%).

D-*Galactose* 6-[N-(p-NN-*Diethylaminophenyl*)*carbamate*].—A solution of the above di-*O*-isopropylidene compound (0·495 g.) in acetic acid (10·0 c.c.) showed α_D^{22} −1·79° (1 dm.). After addition of concentrated hydrochloric acid (10·0 c.c.) the value changed to +0·92° and became constant at +1·09° after 2 hr. The solution was then evaporated under reduced pressure to a glass, which was purified by treatment in ethanol with charcoal, followed by filtration and evaporation, to give the *carbamate hydrochloride* (Found: C, 50·2; H, 7·2; N, 6·3; Cl, 8·7. $C_{17}H_{27}ClN_2O_7$ requires C, 50·2; H, 6·7; N, 6·9; Cl, 8·7%).

Phenyl N-(p-*Carboxyphenyl*)*carbamate* (with B. J. Johnson).—A mixture of phenol (3·8 g.), pyridine (0·1 g.) and methyl *p*-isocyanatobenzoate (7·1 g.), heated for 2 hr. at 100°, gave *phenyl* N-(p-*methoxycarbonylphenyl*)*carbamate* (10·2 g.), m. p. 164—165° (from ethanol) (Found: C, 66·5; H, 4·8. $C_{15}H_{13}NO_4$ requires C, 66·4; H, 4·8%). This ester (6·0 g.) was boiled under reflux for 24 hr. in acetic acid (90 c.c.) and concentrated hydrochloric acid (30 c.c.), and the cooled solution was then diluted with water. The precipitated *acid* formed a microcrystalline powder (3·5 g.) (from acetone), m. p. >300° (Found: C, 64·9; H, 4·5; N, 5·5. $C_{14}H_{11}NO_4$ requires C, 65·35; H, 4·3; N, 5·45%).

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461. *Cytotoxic Compounds. Part III.*[1] *Some Derivatives of* p-(NN-*Di*-2-*chloroethyl- and of* p-(NN-*Di*-2-*bromoethyl-amino*)*thiophenol.*

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Thiolcarbonates, thiolcarbamates, and thiolesters, derived from the above "nitrogen mustards," have been prepared. Some mercurial compounds are also described.

Syntheses of *p*-(*NN*-di-2-chloroethylamino)thiophenol (I) and its dibromo-analogue (II) were described in Part I.[2] In view of the biological results obtained [3] on some of the urethanes described in Part II,[1] it was desirable to prepare analogues (thiolcarbonates and thiolcarbamates) based on the thiols (I) and (II).

The thiolcarbonates (III; Y = Et and Pr^i) and (IV) were readily obtained by reaction of the thiol (I), as potassium salt or in pyridine, with the appropriate chloroformate. The bromo-analogue of the ester (III; Y = Pr^i) was made similarly from the bromo-thiol (II), and also from the chloro-ester (III; Y = Pr^i) by reaction with lithium bromide; the latter method was used to obtain the bromo-analogue of (III; Y = cholesteryl) and of the galactose derivative (IV). Conditions could not be established for the selective removal of the isopropylidene groups in the sugar derivative (IV).

An alternative route to thiolcarbonates of type (III) would be reaction of an alcohol with *p*-(*NN*-di-2-chloroethylamino)phenyl chlorothiolformate (V); the latter reagent

[1] Part II, Benn, Creighton, Owen, and White, preceding paper.
[2] Benn, Owen, and Creighton, *J.*, 1958, 2800.
[3] Danielli, *Ann. Reports British Empire Cancer Campaign*, 1956, **34**, 398; 1957, **35**, 410; 1958, **36**, 527; 1959, **37**, 575.

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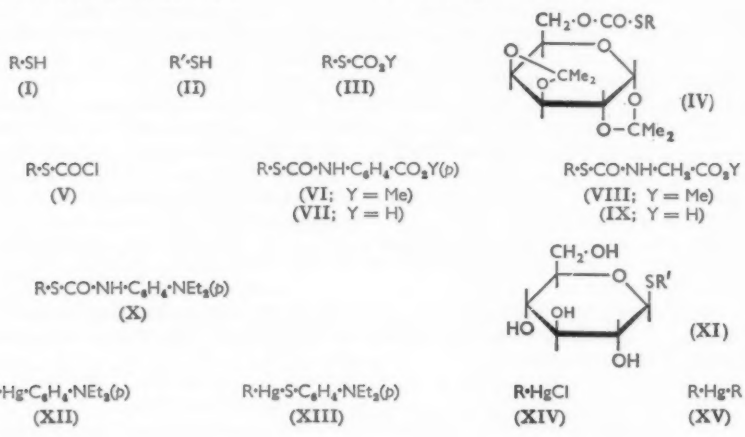
would also be useful in other types of reactions. Although the pure compound could not be isolated, it was prepared as a crude oil by interaction of the thiol (I) and carbonyl chloride in ether. Treatment of a solution of the oil in benzene with propan-2-ol gave the thiolcarbonate (III; Y = Pr^i) identical with that obtained by the other route, whilst reaction with 2,4-dinitrophenol (a metabolic poison) gave the corresponding 2,4-dinitrophenyl ester, a compound which on enzymic fission would yield *two* toxic components.



The desirability of conferring water-solubility on a nitrogen mustard was stressed in the preceding paper, and some of the reagents described there have also been useful in the present connection. Methyl *p*-isocyanatobenzoate reacted with the thiol (I) to give the thiolcarbamate (VI), also obtained from the chlorothiolformate (V) and methyl *p*-aminobenzoate, and by treatment with boiling 1 : 1 hydrochloric–acetic acid it was possible to effect preferential hydrolysis of the methyl ester group to give the acid (VII). Similarly, methyl isocyanatoacetate was used to obtain the ester (VIII) and thence the acid (IX), the bromo-analogue of which was likewise prepared from the bromo-thiol (II) and also by halide-exchange from (IX). The advantage of methyl esters in these syntheses was shown by the fact that the ethyl ester corresponding to (VIII) was much more resistant to hydrolysis, and the free acid (IX) could not be obtained from it, more extensive fission occurring under the more drastic conditions required. The basic thiolcarbamate (X) was prepared by reaction of *p*-*NN*-diethylaminophenyl isocyanate with the thiol (I).

The acetyl, propionyl, and benzoyl derivatives of the bromo-thiol (II), which were required for comparison with the corresponding chloro-compounds derived from (I), were prepared from the latter derivatives by exchange reactions with lithium bromide, a method which usually gave better results than direct acylation of the thiol (II). In the same way the tetra-*O*-acetyl-β-D-glucoside of (II) was obtained from that of (I); solvolytic deacetylation then furnished the glucothioside (XI).

Reaction of the thiol (I) with *p*-*NN*-diethylaminophenylmercuric chloride gave the mercurial (XII). The isomer (XIII) was prepared by condensation of *p*-(*NN*-diethylamino)thiophenol with *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (XIV). The latter reagent, prepared *via* the corresponding mercuric acetate by mercuration of *NN*-di-2′-chloroethylaniline, reacted similarly with thiophenol but behaved differently towards aliphatic thiols; with 2-mercaptoethanol, for instance, the products were the diarylmercury (XV) and di-(2-hydroxyethylthio)mercury, whilst with propane-2-thiol

it gave what appeared to be a mixture of isopropylthiomercuric chloride and di-isopropylthiomercury.

For reasons mentioned before,[1] several non-mustard analogues were prepared in the course of this work, mostly by application of the methods discussed above.

Ross's method [4] was again used to determine the extent of hydrolysis of some of the mustards after 30 min. in boiling 50% aqueous acetone (see Table).

Rates of hydrolysis.

R = *p*-(*NN*-Di-2-chloroethylamino)phenyl. R′ = *p*-(*NN*-Di-2-bromoethylamino)phenyl.

Compound	mmole in acetone (25 c.c.) + water (25 c.c.)	Hydrol. (%) in 30 min. at 66°	Compound	mmole in acetone (25 c.c.) + water (25 c.c.)	Hydrol. (%) in 30 min. at 66°
R·S·CO_2Pr^i	0·3	5	R′·SAc	0·5	26
(IV)	0·5	3	R′·S·COEt	0·5	24
(IV; R′ analogue)	0·3	23	R′·S·COPh	0·3	26
R·S·CO·NH·CH_2·CO_2H	0·3	7	R′·S·(tetra-*O*-acetyl-glucosyl)	0·3	29
R′·S·CO·NH·CH_2·CO_2H	0·4	40			

Experimental

Microanalyses were by Miss J. Cuckney and the staff of the Organic Microanalytical Laboratories.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl Chlorothiolformate* (V).—A solution of *p*-(*NN*-di-2-chloroethylamino)thiophenol [2] (10·0 g.) and pyridine (3·2 g.) in dry ether (250 c.c.) was slowly added (1 hr.) to a stirred solution of carbonyl chloride (10 g.) in ether (250 c.c.) through which carbonyl chloride was continuously passed. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure to an oil (10 g.). This crude chlorothiolformate was characterised by reaction in benzene with aniline to give *p*-(*NN*-di-2-chloroethylamino)-phenyl *N*-phenylthiolcarbamate,[2] m. p. and mixed m. p. 143°.

S-p-(NN-*Di*-2-*chloroethylamino*)*phenyl* O-*Isopropyl Thiolcarbonate* (III; Y = Pr^i).—(i) Isopropyl chloroformate (2·44 g.) in chloroform (10 c.c.) was added to a mixture of *p*-(*NN*-di-2-chloroethylamino)thiophenol (5·0 g.) in chloroform (25 c.c.) and potassium hydroxide (1·2 g.) in ethanol (5 c.c.). The mixture was stirred for 6 hr., and then filtered and concentrated. Recrystallisation of the residue from methanol gave the *thiolcarbonate* (4·5 g., 66%), m. p. 84°, raised to 87° on further recrystallisation (Found: C, 50·7; H, 5·6; N, 4·4. $C_{14}H_{19}Cl_2NO_2S$ requires C, 50·0; H, 5·7; N, 4·2%).

(ii) A saturated solution of sodium isopropoxide in propan-2-ol was added dropwise to a stirred solution of *p*-(*NN*-di-2-chloroethylamino)phenyl chlorothiolformate (4·5 g.) in benzene (100 c.c.) until a test portion, shaken with water, gave an alkaline reaction. The mixture was filtered, and the filtrate was washed with water, dried, and evaporated to a residue which on recrystallisation from methanol gave the thiolcarbonate (4·0 g.), m. p. 79—81°, raised on recrystallisation to 84°.

S-p-(NN-*Di*-2-*bromoethylamino*)*phenyl* O-*Isopropyl Thiolcarbonate*.—(i) Potassium hydroxide (1·6 g.) in ethanol (5 c.c.) was added to *p*-(*NN*-di-2-bromoethylamino)thiophenol [2] (1·0 g.) in chloroform (25 c.c.) at −80° under nitrogen, and a solution of isopropyl chloroformate (0·5 g.) in chloroform (3 c.c.) was added. The mixture was shaken and allowed to warm to room temperature during 3 hr., and was then filtered and evaporated to a solid residue. Recrystallisation from methanol gave the *thiolcarbonate* (0·4 g.), m. p. 103° (Found: C, 39·9; H, 4·7; N, 3·4. $C_{14}H_{19}Br_2NO_2S$ requires C, 39·5; H, 4·5; N, 3·3%).

(ii) A solution of *S*-*p*-(*NN*-di-2-chloroethylamino)phenyl *O*-isopropyl thiolcarbonate (1·45 g.) in isobutyl methyl ketone (20 c.c.), containing lithium bromide (4 g.), was refluxed for 4 hr., then cooled, diluted with chloroform (50 c.c.), washed with water, dried, and concentrated. Recrystallisation of the product from methanol gave the thiolcarbonate (1·0 g.), m. p. 102°.

S-p-(NN-*Di*-2-*chloroethylamino*)*phenyl* O-*Ethyl Thiolcarbonate* (III; Y = Et).—Prepared from the potassium salt of *p*-(*NN*-di-2-chloroethylamino)thiophenol and ethyl chloroformate,

[4] Ross, *J.*, 1949, 183.

as described for the isopropyl ester, the *thiolcarbonate* (yield 73%), after recrystallisation from methanol, had m. p. 73° (Found: C, 48·7; H, 5·6; N, 4·2. $C_{13}H_{17}Cl_2NO_2S$ requires C, 48·45; H, 5·3; N, 4·35%).

S-p-(NN-*Di*-2-*chloroethylamino*)*phenyl* O-(1,2:3,4-*Di*-O-*isopropylidene*-D-*galactose*) 6-*Thiolcarbonate* (IV).—Potassium hydroxide (2·0 g.) in ethanol (50 c.c.), and 1,2:3,4-di-*O*-isopropylidene-D-galactose 6-chloroformate [5] (9·5 g.) were successively added to a solution of *p*-(*NN*-di-2-chloroethylamino)thiophenol (8·9 g.) in chloroform (100 c.c.) under nitrogen. The mixture was stirred for 20 hr., then washed with water, dried, and concentrated to an oil which was taken up in a little hot ethanol and kept at *ca.* 5° overnight. The resulting solid (15·0 g.), m. p. 99—100°, was recrystallised from ethanol to give the *thiolcarbonate* as large rhombs (14·2 g., 74%), m. p. 104—105°, $[\alpha]_D^{23}$ −47° (*c* 5 in $CHCl_3$) (Found: C, 51·8; H, 6·2; Cl, 13·3. $C_{23}H_{31}Cl_2NO_7S$ requires C, 51·5; H, 5·8; Cl, 13·2%), $\lambda_{max.}$ 2730 Å (ε 27,300).

S-p-(NN-*Di*-2-*bromoethylamino*)*phenyl* O-(1,2:3,4-*Di*-O-*isopropylidene*-D-*galactose*) 6-*Thiolcarbonate*.—The preceding thiolcarbonate (4·0 g.), lithium bromide (8·0 g.), and isobutyl methyl ketone (60 c.c.) were heated together at 100° for 6 hr. to give the *dibromo-analogue*, pale yellow rhombs (3·9 g., 84%), m. p. 107—108° [from chloroform–light petroleum (b. p. 40—60°)], $[\alpha]_D^{23}$ −40° (*c* 5 in $CHCl_3$) (Found: O, 17·8; Br, 25·6. $C_{23}H_{31}Br_2NO_7S$ requires O, 17·9; Br, 25·6%), $\lambda_{max.}$ 2750 Å (ε 30,000).

O-*Cholesteryl* S-p-(NN-*Di*-2-*bromoethylamino*)*phenyl Thiolcarbonate*.—Cholesteryl chloroformate [6] (6·0 g.) in chloroform (20 c.c.) was added to a stirred mixture of *p*-(*NN*-di-2-chloroethylamino)thiophenol (3·3 g.) in chloroform (40 c.c.) and potassium hydroxide (0·75 g.) in ethanol (20 c.c.) under nitrogen. The mixture was stirred for 24 hr. and worked up to give an oil, which was treated with lithium bromide (12 g.) in boiling isobutyl methyl ketone (40 c.c.) for 6 hr. The product crystallised when set aside at 0° with ethanol–light petroleum (b. p. 100—120°), and after five recrystallisations from light petroleum (b. p. 60—80°) it gave the *thiolcarbonate* as fibrous needles (2·0 g.), m. p. 115°, $[\alpha]_D^{23}$ −30° (*c* 3 in $CHCl_3$) (Found: Br, 21·2. $C_{35}H_{57}Br_2NO_2S$ requires Br, 21·3%), $\lambda_{max.}$ 2760 Å (ε 29,000).

S-p-(NN-*Di*-2-*chloroethylamino*)*phenyl* O-2,4-*Dinitrophenyl Thiolcarbonate*.—2,4-Dinitrophenol (1·8 g.) in chloroform (50 c.c.) was added to a solution of crude *p*-(*NN*-di-2-chloroethylamino)phenyl chlorothiolformate (3·1 g.) and pyridine (0·8 c.c.) in chloroform (44 c.c.), and the mixture was shaken for 1 hr., then washed with water, dried, and concentrated. Recrystallisation of the residue from acetone–ethanol–light petroleum (b. p. 60—80°) gave a bright yellow powder of the *thiolcarbonate* (2·1 g.), m. p. 117° (Found: C, 44·5; H, 3·6; N, 9·0. $C_{17}H_{15}Cl_2N_3O_6S$ requires C, 44·35; H, 3·3; N, 9·6%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-*Methoxycarbonylphenyl*)*thiolcarbamate* (VI).—(i) Methyl *p*-aminobenzoate (1·0 g.) in dry benzene (60 c.c.) containing pyridine (0·5 c.c.) was added to a stirred solution of *p*-(*NN*-di-2-chloroethylamino)phenyl chlorothiolformate (2·0 g.) in benzene (50 c.c.); the mixture was stirred at 50° for 90 min., and then cooled, washed with water, dried, and evaporated to an oil, which crystallised when triturated with light petroleum (b. p. 40—60°). Recrystallisation from methanol gave cubes of the *thiolcarbamate* (2·0 g., 70%), m. p. 143° (Found: C, 53·35; H, 4·8; Cl, 16·25; S, 8·3. $C_{19}H_{20}Cl_2N_2O_3S$ requires C, 53·4; H, 4·7; Cl, 16·5; S, 7·5%).

(ii) *p*-(*NN*-Di-2-chloroethylamino)thiophenol (5·0 g.) and methyl *p*-isocyanatobenzoate [7] (3·5 g.) were heated together for 4 hr. at 100° in a sealed tube. Recrystallisation of the product from methanol gave the ester (6·6 g., 77%), m. p. and mixed m. p. 138—140°.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-*Carboxyphenyl*)*thiolcarbamate* (VII).—The methyl ester (2·5 g.) was refluxed in 1 : 1 acetic acid–concentrated hydrochloric acid (125 c.c.) for 40 min. and then cooled to 0°. Ice-water (30 c.c.) was added and the precipitate was filtered off and recrystallised from benzene to give the *acid* (1·8 g., 73%), m. p. 175° (Found: N, 7·2; Cl, 17·3. $C_{18}H_{18}Cl_2N_2O_3S$ requires N, 6·8; Cl, 17·2%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* N-(p-*Methoxycarbonylphenyl*)*thiolcarbamate*.—Reaction of *p*-(*NN*-di-2-bromoethylamino)thiophenol (3·05 g.) with methyl *p*-isocyanatobenzoate (1·6 g.) and pyridine (0·1 c.c.) at 100° for 4 hr. gave the *thiolcarbamate* (3·5 g., 76%), m. p. 156°, raised to 161° on further recrystallisation (Found: C, 44·85; H, 4·0; Br, 30·9. $C_{19}H_{20}Br_2N_2O_3S$ requires C, 44·2; H, 3·9; Br, 31·0%).

[5] Haworth, Porter, and Waine, *Rec. Trav. chim.*, 1938, **57**, 541.
[6] Wieland, Honold, and Pascual-Vila, *Z. physiol. Chem.*, 1923, **130**, 326.
[7] Siefken, *Annalen*, 1949, **562**, 75.

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p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Methoxycarbonylmethyl*)*thiolcarbamate* (VIII).—*p*-(*NN*-Di-2-chloroethylamino)thiophenol (5·0 g.) and methyl isocyanatoacetate [1] (2·35 g.) were heated together at 100° for 3 hr. in a sealed tube. Recrystallisation of the product from carbon tetrachloride–light petroleum (b. p. 40—60°) gave the *thiolcarbamate* (5·9 g., 82%), m. p. 79—80° (Found: C, 46·3; H, 5·0. $C_{14}H_{18}Cl_2N_2O_3S$ requires C, 46·0; H, 5·0%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Ethoxycarbonylmethyl*)*thiolcarbamate*.—Prepared in a similar way from *p*-(*NN*-di-2-chloroethylamino)thiophenol (1·0 g.) and ethyl isocyanatoacetate [7] (0·5 g.) the *thiolcarbamate* (1·3 g., 65%), after recrystallisation from ethanol–light petroleum (b. p. 40—60°), had m. p. 82° (Found: C, 47·8; H, 5·2. $C_{15}H_{20}Cl_2N_2O_3S$ requires C, 47·5; H, 5·3%).

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(*Carboxymethyl*)*thiolcarbamate* (IX).—*p*-(*NN*-Di-2-chloroethylamino)phenyl *N*-(methoxycarbonylmethyl)thiolcarbamate (5·7 g.) was refluxed for 4 min. with 1 : 1 acetic acid–concentrated hydrochloric acid (30 c.c.) and then cooled to 0°. Ice-water (80 c.c.) was added, followed by saturated sodium hydrogen carbonate solution to bring the pH to *ca.* 3. The precipitate, after recrystallisation from benzene–light petroleum (b. p. 40—60°) gave the *acid* as plates (4·5 g., 81%), m. p. 105—106° (Found: C, 44·9; H, 4·7; Cl, 20·1. $C_{13}H_{16}Cl_2N_2O_3S$ requires C, 44·45; H, 4·6; Cl, 20·2%).

The ethyl ester, refluxed in 1 : 1 acetic acid–concentrated hydrochloric acid for varying periods, gave either unchanged ester or non-crystallisable oils.

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* N-(*Methoxycarbonylmethyl*)*thiolcarbamate*.—*p*-(*NN*-Di-2-bromoethylamino)thiophenol (1·5 g.) and methyl isocyanatoacetate (0·6 g.) were heated together at 100° for 3 hr. The product was extracted with boiling 1 : 1 chloroform–carbon tetrachloride (25 c.c.), and the solution, decanted from residual oil, was diluted with light petroleum (b. p. 40—60°) to incipient precipitation. Storage overnight at 0° gave a solid which was several times recrystallised from carbon tetrachloride–light petroleum (b. p. 40—60°) to give the *thiolcarbamate* (0·7 g.), m. p. 80—81° (Found: C, 37·3; H, 4·2. $C_{14}H_{18}Br_2N_2O_3S$ requires C, 37·0; H, 4·0%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* N-(*Carboxymethyl*)*thiolcarbamate*.—(i) The above methyl ester (0·6 g.) was refluxed with 1 : 1 acetic acid–concentrated hydrochloric acid (16 c.c.) for 2½ min., then cooled and partly neutralised with 2N-sodium hydroxide (50 c.c.). Extraction with chloroform gave a solid, which on recrystallisation from benzene gave plates (0·35 g., 60%) of the *acid* (containing one mol. of benzene of crystallisation), m. p. 120° (Found: C, 43·75; H, 4·5; Br, 31·0. $C_{13}H_{16}Br_2N_2O_3S,C_6H_6$ requires C, 44·0; H, 4·3; Br, 30·8%).

(ii) A solution of lithium bromide (15 g.) and *p*-(*NN*-di-2-chloroethylamino)phenyl *N*-(carboxymethyl)thiolcarbamate (3·1 g.) in isobutyl methyl ketone (160 c.c.) was heated at 120° overnight. The product, isolated as described for similar reactions above, gave the acid (solvated) (2·75 g., 60%), m. p. 124°.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* N-(p-NN-*Diethylaminophenyl*)*thiolcarbamate* (X).—*p*-*NN*-Diethylaminophenyl isocyanate [1] (3·75 g.) and *p*-(*NN*-di-2-chloroethylamino)thiophenol (5·0 g.), heated together at 100° for 3 hr. in a sealed tube, gave the *thiolcarbamate* (6·4 g., 74%) as solvated needles (from carbon tetrachloride), m. p. 140° (Found: C, 54·0; H, 5·35; Cl, 20·6. $C_{21}H_{27}Cl_2N_3OS,\frac{1}{5}CCl_4$ requires C, 54·0; H, 5·8; Cl, 20·6%). Recrystallisation from benzene–light petroleum (b. p. 40—60°), although less satisfactory, gave the thiolcarbamate, m. p. 140—141°, free from solvent (Found: C, 57·6; H, 5·8; Cl, 15·65. $C_{21}H_{27}Cl_2N_3OS$ requires C, 57·3; H, 6·2; Cl, 16·1%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* *Thiolacetate*.—(i) Reaction of *p*-(*NN*-di-2-chloroethylamino)phenyl thiolacetate [2] (5·0 g.) with lithium bromide (7 g.) in boiling isobutyl methyl ketone (30 c.c.) for 3 hr. gave the *dibromo-compound* (4·5 g., 69%), needles [from light petroleum (b. p. 60—80°)], m. p. 70° (Found: C, 37·7; H, 4·2; Br, 41·8. $C_{12}H_{15}Br_2NOS$ requires C, 37·8; H, 4·0; Br, 41·7%), $\lambda_{max.}$ 2740 Å (ε 26,300).

(ii) Acetylation of *p*-(*NN*-di-2-bromoethylamino)thiophenol with acetic anhydride in pyridine at room temperature gave a poor yield (15%) of the thiolacetate, m. p. 64—66°, undepressed on admixture with the pure ester described above.

p-(NN-*Di*-2-*chloroethylamino*)*phenyl* *Thiolpropionate*.—Prepared in 82% yield by treatment of *p*-(*NN*-di-2-chloroethylamino)thiophenol with propionic anhydride in pyridine at room temperature, the *ester* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 60° (Found: Cl, 23·1. $C_{13}H_{17}Cl_2NOS$ requires Cl, 23·2%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl Thiolpropionate*.—Treatment of the above thiolpropionate with lithium bromide, as described for the thiolacetate, gave needles of the *dibromo-analogue*, m. p. 69° [from light petroleum (b. p. 60—80°)] (Found: Br, 40·5. $C_{13}H_{17}Br_2NOS$ requires Br, 40·45%), $\lambda_{max.}$ 2740 Å (ε 24,900).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl Thiolbenzoate*.—(i) Reaction of *p*-(*NN*-di-2-chloroethylamino)phenyl thiolbenzoate [2] with lithium bromide in boiling isobutyl methyl ketone for 4 hr. gave pale yellow needles (82%) of the *dibromo-analogue*, m. p. 110—111° (from chloroform–ethanol) (Found: C, 46·1; H, 4·0; Br, 36·3. $C_{17}H_{17}Br_2NOS$ requires C, 46·05; H, 3·9; Br, 36·1%), $\lambda_{max.}$ 2390, 2740 Å (ε 14,200, 32,800).

(ii) Benzoylation of *p*-(*NN*-di-2-bromoethylamino)thiophenol with benzoic anhydride in pyridine gave a 60% yield of crude thiolbenzoate, m. p. 103—109°.

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucothioside*.—Prepared by reaction of the dichloro-analogue [2] (4·0 g.) with lithium bromide (8 g.) in boiling isobutyl methyl ketone (25 c.c.) for 5 hr., the compound crystallised from propan-2-ol in prisms (3·5 g., 76%), m. p. 119—120°, $[\alpha]_D^{23}$ −41° (*c* 2 in $CHCl_3$) (Found: O, 21·2; Br, 23·6. $C_{24}H_{32}Br_2NO_9S$ requires O, 21·5; Br, 23·8%).

p-(NN-*Di*-2-*bromoethylamino*)*phenyl* β-D-*Glucothioside* (XI).—Sodium (4 mg.) was added to the above tetra-acetate (1·0 g.) in dry methanol (30 c.c.), and the solution was set aside overnight, then saturated with carbon dioxide and evaporated to dryness. Crystallisation from ethanol–light petroleum (b. p. 40—60°) gave the *glucothioside dihydrate* as needles (0·45 g., 60%), m. p. 90° (Found: O, 20·8; Br, 30·3. $C_{16}H_{23}Br_2NO_5S,2H_2O$ requires O, 20·8; Br, 29·8%).

[p-(NN-*Di*-2-*chloroethylaminophenyl*)*thio*]-(p-NN-*diethylaminophenyl*)*mercury* (XII).—*p*-(*NN*-Di-2-chloroethylamino)thiophenol (4·0 g.) in acetone (16 c.c.) was mixed with *N*-ethanolic sodium ethoxide (15·4 c.c.), and the solution was added to *p*-*NN*-diethylaminophenylmercuric chloride [3] (6·1 g.) in acetone (110 c.c.). The mixture was diluted to 500 c.c. with light petroleum (b. p. 40—60°) and then filtered. The precipitate was washed with water and recrystallised from acetone to give the *mercurial* (4·4 g., 47%), m. p. 126—127° (Found: C, 40·5; H, 4·6; S, 5·7. $C_{20}H_{26}Cl_2HgN_2S$ requires C, 40·2; H, 4·4; S, 5·4%), $\lambda_{max.}$ 3000 Å (ε 31,400).

p-(NN-*Di*-2-*chloroethylamino*)*phenylmercuric Chloride* (XIV).—A hot solution of mercuric acetate (30 g.) in ethanol (300 c.c.) was added to *NN*-di-2′-chloroethylaniline [2] (20 g.) in ethanol (100 c.c.), and the mixture was set aside for 3 hr. and then cooled to 0°. The solid was collected and recrystallised from acetone, containing a few drops of acetic acid, to give needles of p-(NN-*di*-2-*chloroethylamino*)*phenylmercuric acetate* (32 g., 72%), m. p. 141° (Found: C, 30·4; H, 3·3. $C_{13}H_{15}ClHgNO_2$ requires C, 30·2; H, 3·2%). This acetate (28 g.) was added to a hot solution of lithium chloride (6 g.) in ethanol (500 c.c.). After 2 hr. the mixture was boiled and filtered hot to give, on cooling, needles of p-(NN-*di*-2-*chloroethylamino*)*phenylmercuric chloride* (21 g., 79%), m. p. 154—155°, raised to 156° on further recrystallisation from ethanol (Found: C, 26·7; H, 3·1. $C_{10}H_{12}Cl_3HgN$ requires C, 26·5; H, 2·7%).

[p-(NN-*Di*-2-*chloroethylamino*)*phenyl*]-[p-(NN-*diethylaminophenyl*)*thio*]*mercury* (XIII).—N-Ethanolic sodium ethoxide (10·0 c.c.) was added to *p*-(*NN*-diethylamino)thiophenol [2] (2·0 g.) in ethanol (7·0 c.c.), and the solution was poured into a stirred solution of *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (4·5 g.) in acetone (40 c.c.). The mixture, now containing a yellow precipitate, was diluted to 100 c.c. with light petroleum (b. p. 40—60°) and filtered. The solid was washed with water and recrystallised from acetone to give the *mercurial* (3·6 g., 60%), m. p. 66—67° (Found: C, 40·9; H, 4·5; S, 5·2. $C_{20}H_{26}Cl_2HgN_2S$ requires C, 40·2; H, 4·4; S, 5·4%), $\lambda_{max.}$ 2900 Å (ε 37,400).

[p-(NN-*Di*-2-*chloroethylamino*)*phenylthio*](*phenyl*)*mercury*.—A solution of thiophenol (0·2 g.) in N-ethanolic sodium ethoxide (2·0 c.c.) was added to *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (0·9 g.) in warm acetone (10 c.c.). The solution was then diluted with water (50 c.c.), and the precipitate was collected and recrystallised from acetone–methanol to give the *mercurial* (0·9 g.) as fibrous needles, m. p. 99—100° (Found: C, 36·5; H, 3·6; N, 2·7. $C_{16}H_{17}Cl_2HgNS$ requires C, 36·5; H, 3·25; N, 2·7%).

Di-[p-(NN-*di*-2-*chloroethylamino*)*phenyl*]*mercury*.—(i) A solution of *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (0·6 g.) in pyridine (4 c.c.) was refluxed over copper powder (0·8 g.) under nitrogen for 20 min. and then cooled, diluted with ether (20 c.c.), and shaken with 2N-sulphuric acid (15 c.c.). The dried ether layer on evaporation gave a solid which on

[3] Whitmore, Hanson, and Carnahan, *J. Amer. Chem. Soc.*, 1929, **51**, 894.

recrystallisation from aqueous acetone formed needles of the *mercurial* (0·25 g., 60%), m. p. 132° (Found: C, 37·8; H, 4·1; N, 4·7. $C_{20}H_{24}Cl_4HgN_2$ requires C, 37·8; H, 3·8; N, 4·4%).

(ii) A solution of *p*-(*NN*-di-2-chloroethylamino)phenylmercuric chloride (0·90 g.) in acetone (10 c.c.) was added to 2-mercaptoethanol (0·16 g.) in N-ethanolic sodium ethoxide (2·0 c.c.). The mixture was diluted with water to 50 c.c. to precipitate an oil which gradually crystallised. Recrystallisation of a portion from aqueous acetone gave the above diarylmercury, m. p. 132°. Recrystallisation of another portion from acetone–light petroleum (b. p. 40—60°) gave di-(2-hydroxyethylthio)mercury, m. p. 119—121° (lit.,[9] m. p. 123°) (Found: C, 13·4; H, 3·4. Calc. for $C_4H_{10}HgO_2S_2$: C, 13·5; H, 2·8%).

Reaction of p-(NN-*Di*-2-*chloroethylamino*)*phenylmercuric Chloride with Propane*-2-*thiol*.—Propane-2-thiol (0·75 g.) in benzene (15 c.c.) was added to *p*-(*NN*-di-2-chloroethylamino)-phenylmercuric chloride (0·45 g.) in ethanol (5 c.c.) and benzene (50 c.c.) at 35°, and the mixture was refluxed for 15 min. and then cooled. Recrystallisation of the precipitated solid from ethanol–dioxan gave a product of m. p. *ca.* 220° (decomp.), probably a mixture of isopropylthiomercuric chloride and di-isopropylthiomercury (Found: C, 12·5; H, 2·6; Cl, 7·5. Calc. for C_3H_7ClHgS: C, 11·6; H, 2·3; Cl, 11·4. Calc. for $C_6H_{14}HgS_2$: C, 20·55; H, 4·0; Cl, 0·0%).

OS-*Diphenyl Thiolcarbonate*.—Phenyl chloroformate (3·1 g.) in chloroform (5 c.c.) was added to a mixture of thiophenol (2·2 g.) in chloroform (20 c.c.) and potassium hydroxide (1·1 g.) in ethanol (15 c.c.). The mixture was shaken for 2 hr., filtered, and evaporated to an oil which crystallised from ethanol to give needles of *diphenyl thiolcarbonate* (1·5 g.), m. p. 62° (Found: C, 68·4; H, 4·6. $C_{13}H_{10}O_2S$ requires C, 67·8; H, 4·4%).

O-*Isopropyl* S-*Phenyl Thiolcarbonate*.—Prepared in a similar way from isopropyl chloroformate (7·3 g.) and thiophenol (6·4 g.) this *ester* was an oil, b. p. 78—80°/1 mm., n_D^{20} 1·5436 (Found: C, 60·8; H, 6·2; S, 16·6. $C_{10}H_{12}O_2S$ requires C, 61·2; H, 6·2; S, 17·0%).

S-*Isopropyl* S-*Phenyl Dithiolcarbonate*.—Phenyl chlorothiolformate [10] (1·7 g.) was added to propane-2-thiol (0·75 g.) and pyridine (0·8 g.). The mixture was diluted with benzene (15 c.c.), washed with water, dried, and distilled to give the *dithiolcarbonate*, b. p. 84—85°/0·1 mm., n_D^{18} 1·5920 (Found: C, 56·4; H, 6·1; S, 29·7. $C_{10}H_{12}OS_2$ requires C, 56·6; H, 5·7; S, 30·2%).

Phenyl N-(*Methoxycarbonylmethyl*)*thiolcarbamate*, prepared by reaction of thiophenol and methyl isocyanatoacetate at 100°, crystallised from methanol in flat needles, m. p. 117—118° (Found: C, 53·1; H, 5·1. $C_{10}H_{11}NO_3S$ requires C, 53·3; H, 4·9%).

p-(NN-*Diethylamino*)*phenyl* N-(*Methoxycarbonylmethyl*)*thiolcarbamate*, prepared by reaction of *p*-(*NN*-diethylamino)thiophenol with methyl isocyanatoacetate at 100°, after recrystallisation from carbon tetrachloride–light petroleum (b. p. 40—60°) had m. p. 67° (Found: C, 56·7; H, 6·75; N, 9·65. $C_{14}H_{20}N_2O_3S$ requires C, 56·7; H, 6·8; N, 9·45%).

p-(NN-*Diethylamino*)*phenyl* N-(*Carboxymethyl*)*thiolcarbamate*.—The above methyl ester (5·2 g.) was refluxed with a 1 : 1 mixture of acetic acid and concentrated hydrochloric acid (35 c.c.) for 3 min. and then cooled to 0°, diluted with water (50 c.c.), and partly neutralised with 2N-sodium hydroxide (150 c.c.). Extraction with chloroform gave the acid as an oil. The *piperidine* salt, recrystallised from nitromethane, had m. p. 108° (Found: C, 58·2; H, 7·6; N, 10·9. $C_{15}H_{29}N_3O_3S$ requires C, 58·8; H, 7·95; N, 11·4%).

Phenyl N-(p-NN-*Diethylaminophenyl*)*thiolcarbamate*.—A solution of phenyl chlorothiolformate (3·45 g.) and *NN*-diethyl-*p*-phenylenediamine (from 4·0 g. of hydrochloride) in ether (150 c.c.) was refluxed for 10 min., then cooled, shaken with saturated aqueous sodium hydrogen carbonate (125 c.c.), and extracted with ether to give the *thiolcarbamate* (2·5 g.), m. p. 80—81° [from light petroleum (b. p. 60—80°)] (Found: C, 67·5; H, 6·8. $C_{17}H_{20}N_2OS$ requires C, 67·95; H, 6·7%).

The product (1·5 g.) was boiled with methyl iodide (35 c.c.) for 5 hr. Dilution with ether, and recrystallisation of the precipitate from methanol–ether gave the *methiodide* (1·3 g.), m. p. 187° (Found: C, 48·4; H, 5·3. $C_{16}H_{23}IN_2OS$ requires C, 48·85; H, 5·2%).

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[9] Bennett, *J.*, 1922, **121**, 2139.
[10] Rivier, *Bull. Soc. chim. France*, 1907, **1**, 733.

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462. *The Infrared Absorption of ^{18}O-Labelled Benzoic Acid, Benzoyl Chloride, and Methyl Benzoate.*

By S. Pinchas, David Samuel, and Marta Weiss-Broday.

The infrared absorptions of ^{18}O-labelled, monomeric benzoic acid, benzoyl chloride, and methyl benzoate (Ph·C^{18}O·^{16}OMe), of about 90 atom % ^{18}O, have been measured in the 3700—670 cm.$^{-1}$ region in comparison with the absorptions of the corresponding normal compounds. The molar extinction coefficients of the C=^{18}O stretching bands of benzoic acid and methyl benzoate, as well as the respective relative integrated absorption intensities, were found to be considerably lower than the corresponding coefficients and intensities of the normal compounds. The decrease in each case seems to be more than can be expected on the basis of the change in frequency only. The splitting of the benzoyl chloride C=O band was found to persist in the spectrum of the labelled compound and was shown to be the result of Fermi resonance.

It was shown recently [1] that the absorption intensity of the X=O group stretching bands (X = C or P), in a number of compounds, is changed appreciably when ^{18}O is substituted for ^{16}O. This effect is by far stronger than could be expected from the usual isotope effect [2] on the intensity of infrared bands, and its origin is as yet unclear. It seemed therefore interesting to investigate the infrared spectra of more compounds, of various classes, containing such groups labelled with ^{18}O and to compare them with the spectra of the corresponding normal substances. This has now been done for [$^{18}O_2$]benzoic acid, [^{18}O]-benzoyl chloride, and methyl [*carbonyl*-^{18}O]benzoate, the results being reported below.

^{18}O-*Labelled Benzoic Acid.*—When carbon tetrachloride solutions of benzoic acid were examined it was found that even solutions as dilute as 0·029 g./l. (0·0002M) are still mainly dimeric. In the case of normal benzoic acid the CO stretching bands are then located at 1739 (due to the monomer) and 1690 cm.$^{-1}$ (stronger; due to the dimer). In the case of Ph·C$^{18}O_2$H of about 90% purity these bands appear at 1707 and 1670 cm.$^{-1}$ respectively. The isotopic difference of 32 cm.$^{-1}$, observed in the C=O stretching frequency of monomeric benzoic acid dissolved in carbon tetrachloride, can be compared with the difference of 29 cm.$^{-1}$ in the analogous case of benzophenone [1a] and the value of 24 cm.$^{-1}$ for benzamide.[1c] That this difference amounts only to 20 cm.$^{-1}$ in the case of dimeric benzoic acid (in CCl_4) is probably the result of the greater participation of other groups, besides the C=O group, in the 1690—1670 cm.$^{-1}$ dimer vibration.

In order to compare the absorption intensity of the pure monomeric [^{18}O]benzoic acid CO band with that of the normal monomer, dilute solutions of these substances in chloroform were prepared. In this solvent benzoic acid is already practically fully dissociated in concentrations of about 0·06 g./l. and only one CO band appears then in the infrared spectrum. This behaviour is due to the tendency of chloroform to form hydrogen-bonded solvates [3] with proton acceptors (such as substances containing carbonyl groups) which stabilise the monomeric form. The CO frequency of normal benzoic acid under these conditions was found at 1715 cm.$^{-1}$ and that of [^{18}O]benzoic acid at 1688 cm.$^{-1}$. The somewhat lower difference between the isotopic monomeric frequencies in chloroform (27 cm.$^{-1}$) than in carbon tetrachloride (32 cm.$^{-1}$), although at the limit of the experimental error, seems to be real and to reflect a stronger chloroform-solvation effect on the normal monomer (—24 cm.$^{-1}$) than on the ^{18}O-labelled one (—19 cm.$^{-1}$). A similar phenomenon

[1] Halmann and Pinchas, *J.*, 1958, (*a*) 1703, (*b*) 3264; (*c*) Pinchas, Samuel, and Weiss-Broday, *J.*, 1961, 1688.
[2] Crawford, *J. Chem. Phys.*, 1952, **20**, 977.
[3] Jones and Sandorfy in "Technique of Organic Chemistry," Interscience Publ., Inc., New York, 1956, Vol. IX, pp. 298—299.

was observed with normal and [^{18}O]benzamide [1c] where the isotopic CO frequency differences are 24 cm.$^{-1}$ in carbon tetrachloride and 20 cm.$^{-1}$ in chloroform.

These values for the CO vibration of benzoic acid compare favourably with the data published by Mecke,[4] *i.e.*, bands at 1757 and 1712 cm.$^{-1}$ for the vapour and at 1742 and 1695 cm.$^{-1}$ for a very dilute carbon disulphide solution.

The high dilution necessary, even in chloroform, to obtain the full disssociation of benzoic acid made it impossible to observe properly any other monomeric infrared absorption band.

The CO band absorption intensities in various solutions of the normal and the labelled acid are summarised in Table 1. The relative integrated absorption intensity of the band in each case was obtained by multiplying the apparent maximum molar extinction coefficient by the apparent half-width of the band.

TABLE 1. *The absorption intensity of the* CO *band in isotopic benzoic acids.*

Material	Concn.[a] (g./l.)	Optical density	Molar extinction coeff. (l. mole^{-1} cm.$^{-1}$)	Half-width (cm.$^{-1}$)	Relative integrated absorption (l. mole^{-1} cm.$^{-2}$)
Normal	0·036	0·232	393	49	19,300
Normal	0·0646	0·403	380	49	18,600
Normal	0·083	0·510	374	49	18,300
90 Atom % ^{18}O ...	0·0354	0·177	350[b]	48·5	17,000
90 Atom % ^{18}O ...	0·069	0·347	352[b]	49	17,200
90 Atom % ^{18}O ...	0·0712	0·360	354[b]	—	—

[a] The solvent is always chloroform, and the cell thickness 20 mm. [b] Corrected for the lower concentration of the labelled acid.

TABLE 2. *The infrared absorption bands of normal and* [^{18}O]*benzoyl chloride* (*cm.*$^{-1}$).

Normal compound				Normal compound			
Present work[a]	Rasmussen and Brattain [5]	Documentation of Molecular Spectra [6]	Labelled compound Present work[b]	Present work[a]	Rasmussen and Brattain [5]	Documentation of Molecular Spectra [6]	Labelled compound Present work[b]
3075w	3081w	*c*	3065w	1175s	1176m	1175[e]	1174vs
*1777*s[d]	*1773*m	1764[e]	1747s[d]	—	1102w		—
1736s	1736m	1721[e]	*1711*s	—	1079w		—
1595w	1599w		1597w	—	1028w		1027w
—	1586w		1582w	—	1003w		—
—	1493w		—	932w	936w		934w
1453w	1450m		1452m	875vs	876vs	871[e]	872vs[b]
—	1418w		—	801w[e]			801w[e]
—	1387w		—		833—714bs		777vs,[e] 769vs,[e]
—	1344w		1342w	774s[e]			758w[e]
1316w	1316w		1314w	{690vs[e]	686s		691vs[e]
—	1304w		—	{685vs[e]			685vs[e]
			1238vw	{676vs[e]	674s	675[e]	676vs[e]
1203s	1204s	1205[e]	1199vs	{671vs[e]			671vs[e]

[a] Unless otherwise stated, for a 3% concentration in CCl_4 in a 0·2 mm. cell. [b] Unless stated differently, for a 9% CCl_4 solution in the same cell. [c] Only the main frequencies are given. [d] The main component of the doublet is italicised. [e] Measured on a capillary layer of pure material. [f] Evidently, this number was intended by the misprinted value of 845, as can be seen from the curve.

Table 1 shows that while the value for the relative integrated absorption intensity of the carbonyl stretching frequency is 18,800 $\pm$ 500 units in the case of the normal acid, it decreases to 17,000 $\pm$ 400 units in the case of the fully ^{18}O-labelled benzoic acid. This decrease of about 10% seems to be more than can be expected from the usual isotopic effect on the intensity of infrared bands (which would seem to be about 3% since [1b] $1688^2/1715^2 = 0{\cdot}97$).

It is interesting that the ^{18}O-labelled benzoic acid behaves as do labelled benzophenone [1a] and triphenylphosphine oxide,[1b] which also show a decrease in the intensity

[4] Mecke, "Documentation of Molecular Spectra Catalogue," Butterworths, London, 1958, compound cards nos. 3183, 3386.

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of their X=^{18}O bands as compared with the normal intensity, and not as does [^{18}O]-benzamide [1c] which in carbon tetrachloride solution absorbs some 20% more than [^{16}O]benzamide while in chloroform solution its intensity is practically that of the normal amide.

[^{18}O]*Benzoyl Chloride.*—The infrared absorption spectrum of both normal benzoyl chloride and 89·9 atom % [^{18}O]benzoyl chloride was investigated for carbon tetrachloride solutions and, in the 830—670 cm.$^{-1}$ region, for undiluted capillary layers. The results are summarised in Table 2 where the literature data concerning the absorption of a 5% carbon tetrachloride solution of normal benzoyl chloride [5] and an undiluted capillary layer of it [6] are included for comparison. As can be seen from this Table the agreement between the present results for normal benzoyl chloride and the literature is very good although some weak bands reported by Rasmussen and Brattain [5] are missing for our chloride. This is, no doubt, partly a consequence of the somewhat lower concentration–cell thickness factor in the present work (3% × 0·2 mm.) relative to that in the case of Rasmussen and Brattain (5% × 0·15 mm.). It can also be noticed that a number of strong bands have now been shown to possess some structure.

When the spectrum of the labelled chloride is compared with that of the normal compound it is observed that the only real differences between them are in the *1777*, **1736**, and **1203** cm.$^{-1}$ frequencies of the normal substance, their values in the case of the labelled modification being **1747**, *1711*, and **1199** cm.$^{-1}$, respectively. Thus, only these frequencies (down to 670 cm.$^{-1}$) are connected with modes of vibration in which the oxygen atom participates considerably.

It is known that the C=O stretching band of aliphatic acid chlorides appears [7] at about 1800 cm.$^{-1}$ and it is equally well established that a phenyl ring conjugated with a carbonyl group usually decreases its otherwise expected frequency by about [8] 20—40 cm.$^{-1}$; hence the C=O stretching band of the normal benzoyl chloride must be expected to appear at about 1770 cm.$^{-1}$. The fact that two bands, at about 1777 and 1736 cm.$^{-1}$, appear in its spectrum in this region has been ascribed by Rasmussen and Brattain [5] to either a monomer–dimer equilibrium or the presence of some low-energy thermally excited level in the chloride.

It was, however, observed that changing the concentration from 0·03 to 0·006 g./l. did not change materially the intensity ratio of the two bands in the case of a cyclohexane solution. This ratio (of about 2 : 1) was also found to be practically constant when different solvents, such as cyclohexane, carbon tetrachloride, and acetonitrile, were used. It was finally established that varying the cell temperature from 20° to 60° had no measurable effect on the relative intensities of the bands. It is therefore clear that this doublet is the result neither of a monomer–dimer equilibrium (which should be affected considerably by changes in dilution and temperature) nor of a thermally excited level (which is more populated at higher temperatures, so that its effect is then more pronounced).

It seems that this doublet is due rather to Fermi resonance between the first overtone of the 875 cm.$^{-1}$ frequency and the fundamental C=O stretching frequency, which probably occur originally at about 1748 and 1765 cm.$^{-1}$, respectively. The higher frequency, being also the more strongly absorbed, thus appears to possess a higher contribution from the original C=O stretching vibration than the lower frequency which has a higher overtone character.

The strong 875 cm.$^{-1}$ band must be attributed to the =C–Cl stretching vibration. This assignment is supported by the strong carbonyl chloride C–Cl band at about [9] 850 cm.$^{-1}$

[5] Rasmussen and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1078.
[6] Collection of the British Ministry of Supply, ref. 4, no. 535.
[7] Ref. 3, p. 457.
[8] Ref. 3, pp. 448, 452, 454, 456.
[9] National Academy of Sciences–National Bureau of Standards, "Infrared Spectral Catalog," compound card no. 831.

and the intense bands at about 900 cm.$^{-1}$ of propionyl chloride,[10] butyryl chloride,[11] and adipoyl chloride.[12]

As mentioned, ^{18}O-labelled benzoyl chloride also shows such a doublet at 1747 and 1711 cm.$^{-1}$; in this case, however, the relative intensity of the two branches is inverted, the lower being now the stronger. It is clear that because of the isotopic exchange the original C=O stretching frequency is decreased here by about [1a] 30 cm.$^{-1}$ and occurs at approximately 1730 cm.$^{-1}$. The original overtone of the C–Cl band of the labelled chloride can be expected to be at about 1740 cm.$^{-1}$ ($= 2 \times 872$ — an anharmonicity correction), so again Fermi resonance between these two vibrations sets in; in this case, however, the lower frequency has a larger contribution from the C=O stretching vibration and is therefore absorbed more readily, giving rise to a stronger band. That the higher frequency of the [^{18}O]chloride appears already at 1747 cm.$^{-1}$, and not higher, seems to imply that its original position is really at about 1732 cm.$^{-1}$, the perturbation shift being about 15 cm.$^{-1}$ (~1730 — 1711). This means a higher anharmonicity term for the C–Cl group in the labelled compound than in the normal substance, the C–Cl overtone of which must be assumed to occur only at about 1748 cm.$^{-1}$ (since the Fermi resonance which increases so much the intensity of the normal overtone must have also affected appreciably its frequency and moved it considerably towards lower frequencies; if it then appears finally at 1736 cm.$^{-1}$ it must have been originally at a materially higher frequency).

The strong band which appears in the normal chloride spectrum at 1203 cm.$^{-1}$ and in the case of the labelled material at 1199 cm.$^{-1}$ is probably analogous to the R·CO·R_1 asymmetrical stretching band which appears in the neighbourhood of 1200 cm.$^{-1}$ in the spectra of ketones,[13,14] propionyl chloride [10] (1250 cm.$^{-1}$), butyryl chloride [11] (1220), adipoyl chloride [12] (1170), etc.

Since neither the 1777 nor the 1711 cm.$^{-1}$ band is due to a pure C=O stretching vibration it is not possible to learn much from a comparison of their absorption intensity. An estimate of this intensity which was however carried out gave the value of 322 l. mole^{-1} cm.$^{-1}$ for the molar extinction coefficient of the (normal) 1777 cm.$^{-1}$ band, and 228 units for the corresponding constant in the case of the 1711 cm.$^{-1}$ (labelled) band.

Methyl [carbonyl-$^{18}O_1$]*Benzoate.*—The infrared absorption of methyl [*carbonyl*-$^{18}O_1$]-benzoate (84 atom % of the C=O oxygen ^{18}O) was investigated in solution in carbon tetrachloride and compared with the absorption of the normal compound under the same conditions. The results are summarised in Table 3, together with other data on the infrared absorption of a pure (liquid) sample of normal methyl benzoate.[5,15]

It is evident from Table 3 that, when the somewhat different measurement conditions are taken into due account, the agreement of the present results for the normal methyl benzoate with those of the literature is generally good (especially with the D.M.S.[15] data).

A comparison of the spectrum of the labelled compound with that of the normal ester shows that the significant differences between them are as follows: (*a*) the C=O stretching band appears at 1696 (C=^{18}O) as compared with 1727 cm.$^{-1}$; (*b*) the =C–OC asymmetrical stretching band [16] at 1277 cm.$^{-1}$ is decreased in the labelled compound to 1273 cm.$^{-1}$; (*c*) new bands appear at 1252, 758, and 702 cm.$^{-1}$ and a band at 822 cm.$^{-1}$ disappears in the isotope spectrum; (*d*) the second benzoate band [17] (at 1111 cm.$^{-1}$), which is probably due to a =C–OC symmetrical stretching vibration,[16] is moved to 1108 cm.$^{-1}$ and the band at 675 cm.$^{-1}$ is shifted to 671 cm.$^{-1}$.

[10] Ref. 9, no. 1687.
[11] Ref. 9, no. 1689.
[12] Ref. 9, no. 1694.
[13] Ref. 3, pp. 507—508.
[14] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen & Co. Ltd., 2nd edn., London, 1958, p. 132.
[15] Collection of the Research Dept., Imperial Chemical Industries Limited, ref. 4, no. 1043.
[16] Ref. 3, p. 503.
[17] Ref. 14, p. 191.

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The shift in the C=O frequency because of the isotopic substitution amounts thus to 31 cm.$^{-1}$, in good agreement with the value of 30 cm.$^{-1}$ observed by Braude and Turner [18] with labelled cinnamyl *p*-nitrobenzoate. The weak band observed in the case of the labelled ester at 1727 cm.$^{-1}$ belongs no doubt to the 16 atom % of normal ester present in it.

The appearance of the new bands and disappearance of the 822 cm.$^{-1}$ band seem to be

TABLE 3. *The infrared absorption bands of normal and* ^{18}O*-labelled methyl benzoate (cm.*$^{-1}$*).*

Normal compound				Normal compound			
Rasmussen and Brattain [5a]	Documentation of Molecular Spectra [15a]	Present work [b]	Labelled compound Present work [c]	Rasmussen and Brattain [5a]	Documentation of Molecular Spectra [15a]	Present work [b]	Labelled compound Present work [c]
3623w	—	—	—	1282vs	1277	1277vs	1273vs
3436w	—	—	—	1220w	—	—	1252w
3077w	3085	—	—	1195m	1190	1192w	1192w
3040m	3060, 3040	3030w	3025w	1179m	1174	1177w	1177w
2985w	2970	2950w	2960w	1161w		—	—
2874w	2870	—	2840w	~1111vs	1108	1111m	1108s
2096w	~2080	—	—	1074s	1068	1069w	1070w
1931w	~1924	—	—	1028s	1025	1028w	1028w
1789w	~1786	—	—	1004w	1000	1006vw	—
1724s	1725	1727s	1727w	969s	964	971w	969w
1684w		—	1696s	940m	932	934vw	934w
1650w	1645	—	—	851w	~845	848vw	
1602w	1607	1602w	1603w	825m	821	822m [a]	—
1590w	1585	~1590vw	~1585w	812w	804	808w [a]	808m [a]
1495w	1496	~1490w	~1490w	762w	—	—	758w [a]
1445s	1456, 1437	1455w, 1436w	1438m	714vs	707	712vs,[a] 707vs [a]	713vs,[a] 707vs,[a] 702vs [a]
1318m	1315	1314w	1313m	689m	685	686m [a]	686m [a]
				676m	672	675m [a]	671m [a]

[a] Measured on a pure liquid. [b] Unless otherwise stated, measured on a 0·016 g./ml. CCl_4 solution in a 0·2 mm. cell. [c] Unless stated differently, measured with a 0·055 g./ml. CCl_4 solution in a 0·2 mm. cell.

due to a different rotational isomeric composition of the different isotopic modifications. Anyhow, the 1252 cm.$^{-1}$ band seems to be connected with some kind of =C–OC vibrations (in analogy with the 1277 cm.$^{-1}$ band), while the 822, 758, and 702 cm.$^{-1}$ bands appear to be a result of some out-of-plane C_{ar}–H bending vibrations similarly to the 800 cm.$^{-1}$ band of benzamide.[1c] The 675 cm.$^{-1}$ band (of the normal ester) must be ascribed to an out-of-plane CO_2 bending vibration, in analogy with the 667 cm.$^{-1}$ CO_2 bending frequency,[19] since it is affected considerably by the isotopic exchange. Ethyl acetate also shows a band in this vicinity [20] (at 630 cm.$^{-1}$), both monomeric and dimeric acetic acid show an absorption maximum at about [21] 670 cm.$^{-1}$, and even the dimer of fully deuterated acetic acid shows this band (at about 645 cm.$^{-1}$).

In spite of the other differences in the infrared spectrum of the labelled ester the decrease in the C=O frequency can no doubt be considered as the only really important one since it is the only change which affects a strong band by more than 5 cm.$^{-1}$. It seems therefore justified to ignore other frequencies in the spectrum when dealing, to a first approximation only, with the problem of the infrared absorption intensity of isotopic modifications of methyl benzoate. Only the absorption intensity of the C=O band of the methyl benzoates was therefore studied. The results of this study, which include the molar extinction coefficient, the band half-width, and the relative integrated absorption intensity in each case, are given in Table 4.

[18] Braude and Turner, *Chem. and Ind.*, 1955, 1223.
[19] Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," Van Nostrand Co. Inc., Princeton, N.J., 1945, p. 274.
[20] Ref. 9, no. 1366.
[21] Herman and Hofstadter, *J. Chem. Phys.*, 1939, **7**, 460.

TABLE 4. *The absorption intensity of the* CO *band in isotopic methyl benzoates.*

Material	Concn. (g./l. CCl_4)	Optical density [a]	Molar extinction coeff. (l. mole^{-1} cm.$^{-1}$)	Band half-width (cm.$^{-1}$)	Relative integrated intensity (l. mole^{-1} cm.$^{-1}$)
Normal	10·77	0·589	372	18·4	6800
Normal	7·42	0·438	401	17·9	7200
84 atom % (C = O)^{18}O	15·24	0·572	308 [b]	20·2	6200
84 atom % (C = O)^{18}O	10·94	0·424	318 [b]	19·8	6300

[a] In a 0·2 mm. cell. [b] Corrected for the content of the normal ester.

As seen from Table 4 the (apparent) molar extinction coefficient of the ester C=O band rises a little with dilution but is still definitely lower for the labelled (313 ± 10 units) than for the normal benzoate (387 ± 15 units). The relative integrated absorption intensity (obtained by multiplying the molar extinction coefficient by the corresponding band half-width) of the ^{18}O-labelled modification is again, as usual, appreciably lower than that of the normal compound. The decrease in integrated intensity, being about 11% (from 7000 ± 200 to 6250 ± 200 units), is in this case also several times that expected from the change in frequency [1b] only (about 3·5%), and methyl benzoate thus falls in line with benzophenone,[1a] triphenylphosphine oxide,[1b] and benzoic acid, leaving benzamide [1c] with its higher C=^{18}O absorption as an exception.

It is noteworthy that, as with triphenylphosphine oxide [1b] and benzamide [1c] dissolved in carbon tetrachloride, the half-width of the X=^{18}O stretching band (as measured in CCl_4) is about 10% bigger than that of the corresponding X=^{16}O band.

The ultraviolet absorption of the labelled methyl benzoate (in ethanol) was also measured and was compared with that of the normal compound. Both spectra were found to show absorption maxima at the same wavelengths, *i.e.*, at 2290 and 2730 Å. However, while the molar extinction coefficient at the first maximum was practically identical in both cases (11,700 ± 150 units in the normal ester, 11,400 ± 200 in the labelled one) it was appreciably different at the second wavelength, being 827 ± 12 units in the normal case and 898 ± 9 units for the isotopic modification. The results reported here for the normal coefficients are in good agreement with those of Ungnade and Lamb [22] (11,000 and 830 units, respectively).

Since the 2730 Å band is due to an $n \rightarrow \pi^*$ C=O transition [23] this difference in its intensity † seems to suggest that the transition moment of this group is somewhat different in the two isotopic modifications.[24] A similar phenomenon, although in the other direction, was observed with the 2530 Å band of benzophenone.[25] These results are in accordance with the other discrepancies in physical properties of isotopic pairs, mentioned above.

EXPERIMENTAL

[$^{18}O_2$]*Benzoic Acid.*—Benzonitrile (8·7 g.) was sealed in a borosilicate tube with water highly enriched in oxygen-18 (40 ml.) and saturated with dry hydrogen chloride. The tube was heated at 100° for 20 hr. After cooling, the water was distilled off and the solid dried *in vacuo* and extracted with dry ether. On recrystallising from ether, [$^{18}O_2$]benzoic acid, m. p. 122°, was obtained in 95% yield. The acid, analysed for its isotopic oxygen content by the method of Anbar and Gutmann,[26] was found to contain 90·0 atom % of oxygen-18.

[^{18}O]*Benzoyl Chloride.*—This compound was prepared by the method of Bender and Ginger [27]

† Since this ester also shows (ref. 22) a shoulder at about 2810 Å it is impossible to evaluate precisely the integrated absorptions of the 2730 Å band and one must compare the molar extinction coefficients instead, assuming the band form to be only little affected by the isotopic exchange.

[22] Ungnade and Lamb, *J. Amer. Chem. Soc.*, 1952, **74**, 3789.
[23] See, *e.g.*, Ito, Inuzuka, and Imanishi, *J. Amer. Chem. Soc.*, 1960, **82**, 1317.
[24] Ref. 19, p. 261.
[25] Halmann and Pinchas, *J.*, 1960, 1246.
[26] Anbar and Gutmann, *J. Internat. Radiation Isotopes*, 1959, **3**, 233.
[27] Bender and Ginger, *J. Amer. Chem. Soc.*, 1955, **77**, 348.

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in which [$^{18}O_2$]benzoic acid (5 g.) was heated with an excess of thionyl chloride (8 ml.) at 100—110° until no further hydrogen chloride was evolved. On fractional distillation, [^{18}O]benzoyl chloride, b. p. 196—198°, was obtained in 90% yield.

On isotopic oxygen analysis the benzoyl chloride was found to contain 89·9 atom % of oxygen-18.

Methyl [carbonyl-$^{18}O_1$]*Benzoate.*—[^{18}O]Benzoyl chloride (2 g.), prepared as above, was dissolved in anhydrous methanol (4 ml.) and boiled gently for 3 hr. until all the hydrogen chloride was driven off.

On fractional distillation at atmospheric pressure methyl [^{18}O]benzoate, b. p. 199—200°, was obtained in quantitative yield. The isotopic oxygen analysis gave 42·0 atom % of oxygen-18, the carbonyl oxygen containing 84 atom % of oxygen-18 and the alkoxy-oxygen being of normal abundance.

Optical Measurements.—The infrared measurements were carried out with a Perkin-Elmer, model 12 C, spectrophotometer equipped with a sodium chloride prism.

The absorption intensity measurements of isotopic pairs of compounds were all made in the same cell and at least in duplicate runs. Their mean result was used in the calculation. Blank measurements on the pure solvent in the same cell were run before each solution measurement.

The ultraviolet measurements were made with a Beckman DU spectrophotometer.

We thank Mr. Joseph Goldberg for assistance with the measurements.

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463. *Aromatic Reactivity. Part XVI.*[1] *Detritiation of Halogenobenzenes.*

By C. EABORN and R. TAYLOR.

We have measured the rates of detritiation of monotritio-benzene and -halogenobenzenes in trifluoroacetic acid containing either aqueous sulphuric acid or aqueous perchloric acid, and have obtained accurate rate factors for detritiation *ortho* and *para* to the halogens, along with rough values for the reaction *meta* to the halogens. Fluorine activates the *para*-position, and the other halogens deactivate this position in the order Cl < I < Br. The halogens deactivate the *ortho*- more than the *para*-position, and deactivate the *ortho*-position in the order F < I < Cl < Br; fluorine, however, deactivates the *ortho*- less than bromine does the *para*-position. The halogens deactivate the *meta*- much more than the *ortho*- and *para*-positions, iodine apparently being the least effective in this deactivation.

The substituent effects are compared with those in other electrophilic aromatic substitutions.

WE have measured the rates of detritiation of monotritiated halogenobenzenes and monotritiated benzene in trifluoroacetic acid containing either aqueous sulphuric acid (at 25·0°) or aqueous perchloric acid (at 55°). The results are given in the Table as first-order rate constants, k_{ex}, and as rates, f, relative to those for [$^3H_1$]benzene. In the case of the medium containing sulphuric acid, the value of k_{ex} is obtained by subtracting from the observed rate of tritium-loss, $k_{obs.}$, the rate of sulphonation $k_{sulph.}$ either measured or estimated (see refs. 2 and 3).

The results represent the first determinations of partial rate factors for the *ortho*- and *para*-positions of halogenobenzenes in hydrogen exchange. The main features of the

[1] Part XV, Eaborn and Taylor, *J.*, 1961, 1012.
[2] Eaborn and Taylor, *J.*, 1960, 3301.
[3] Eaborn and Taylor, *J.*, 1961, 247.

Detritiation of X·C_6H_4·^{3}H.[a]

	CF_3·CO_2H–H_2O–H_2SO_4 (25·0°) (83·40)–(1·98)–(14·62) [b]				CF_3·CO_2H–H_2O–$HClO_4$ (55·0°) (96·77)–(0·82)–(2·41) [b]		CF_3·CO_2H–H_2O–$HClO_4$ (55·0°) (89·50)–(4·55)–(5·95) [b]	
X	$10^7k_{obs.}$	$10^7k_{sulph.}$	10^7k_{ex}	f	10^7k_{ex}	f	10^7k_{ex}	f
H	560	63	497	1	3025	1	12,800	1
p-F	882	22 [c]	860	1·73	5420	1·79	—	—
p-Cl	65·5	2·5	63	0·127	487	0·161	—	—
p-Br	38·5	2·5 [d]	36	0·072	298	0·098	1090	0·085
p-I	45·5	2·5 [d]	43	0·0865	339	0·112	—	—
o-F	—	—	—	—	412	0·136	1610	0·126
o-Cl	—	—	—	—	107	0·035	465	0·036
o-Br	—	—	—	—	83	0·027	350	0·027
o-I	—	—	—	—	129	0·043	525	0·041
m-F	—	—	—	—	—	—	(25)	~0·002
m-Cl	3·42	2·46	1·0	0·002	—	—	(16) [e]	~0·001
m-Br	—	—	—	—	—	—	(16) [e]	~0·001
m-I	—	—	—	—	—	—	(42) [e]	~0·003

[a] Rate constants in sec.$^{-1}$. [b] Mole-percentages in parentheses. [c] It is assumed that fluorobenzene is sulphonated about 9 times as fast as chlorobenzene; the ratio is *ca.* 5 in nitration and *ca.* 11 in molecular chlorination. [d] Iodo- and bromo-benzene are assumed to be sulphonated at about the same rate as chlorobenzene. [e] Rough figures only, see text.

results, including comparisons with data for other electrophilic aromatic substitutions, are as follows:

(i) The spread of rates is dependent upon the medium in the manner previously noted with other aromatic compounds.[1-3] A plot of log f in one medium against log f in either of the other media is a straight line.

(ii) Fluorine clearly activates the *para*-position in detritiation, as it does in molecular bromination and chlorination,[4] the $+T$ effect outweighing the $-I$ effect. In nitration,[5] proto-,[6,7] mercuri-,[8] and bromo-desilylation,[9] and in proto-degermylation,[10] and -destannylation,[11] fluorine deactivates the *para*-position. The activation in detritiation is consistent with the observation that the demand on the electromeric effect of substituents is large in this reaction.[1] (Because a *p*-Bu^t group activates more than a *p*-Me group in detritiation in media of the type used in the present work, we previously suggested that demand on $+E$ effects of substituents might not be large, in spite of large values of f_p^{Me} which would normally be associated with a strong call on polarizability effects.[3] Results from detritiation of [$^3H_1$]biphenyls and [$^3H_1$]naphthalenes,[1] and now of *p*-[$^3H_1$]fluorobenzene, show clearly that the demand on $+E$ effects *is* large. The difficulty of explaining the activation order *p*-Bu^t > *p*-Me in terms of electrical effects of substituents only is thus even greater than we had indicated.[3])

Additional results for the *p*-F atom, not shown in the Table, are that it activates 2·18 times in 76·29 wt.-% aqueous sulphuric acid, in which *p*-Me activates 240 times,[2] 1·7 times in CF_3·CO_2H (92·04)–H_2O (5·45)–$HClO_4$ (2·51) in which *p*-Me activates 313 times,[3] and 2·4 times in CF_3·CO_2H (85·08)–H_2O (6·42)–H_2SO_4 (8·50) in which *p*-Me activates 540 times. It seems that the value of f for *p*-F does not necesarily rise with f for *p*-Me.

(iii) The deactivation order *p*-Cl < *p*-I < *p*-Br applies in detritiation, as in molecular bromination (of 3-halogeno-1,2,4,5-tetramethylbenzenes) in nitromethane.[12] In nitration, *p*-I is several times less deactivating than *p*-Cl and *p*-Br substituents,[13] and this has been

[4] de la Mare and Ridd, "Aromatic Substitution, Nitration and Halogenation," Butterworths Scientific Publ., London, 1959, pp. 138—139.
[5] Bird and Ingold, *J.*, 1938, 918.
[6] Eaborn, *J.*, 1956, 4858.
[7] Deans and Eaborn, *J.*, 1959, 2299.
[8] Eaborn and Webster, unpublished work.
[9] Eaborn and Webster, *J.*, 1957, 4449; 1960, 179.
[10] Eaborn and Pande, *J.*, 1961, 297.
[11] Eaborn and Waters, *J.*, 1961, 542.
[12] Illuminati and Marino, *J. Amer. Chem. Soc.*, 1956, **78**, 4975.
[13] Roberts, Sanford, Sixma, Cerfontain, and Zagt, *J. Amer. Chem. Soc.*, 1954, **76**, 4525.

attributed either to a small demand on electromeric effects,[14] or to a large demand on inductomeric effects made by a positively charged reagent.[15,16] However, the demand on electromeric effects is probably even smaller in proto-desilylation and -degermylation, in which *p*-I deactivates more than *p*-Cl, and moreover, in these reactions, as in detritiation, a positively charged reagent is involved. The deactivation order *p*-I < *p*-Cl < *p*-Br applies in molecular bromination (of 1-halogenonaphthalenes [16]) and possibly in molecular chlorination; [17] these are reactions with a large electron-demand, and the *p*-chloro-atom, with its larger $+E$ effect, might have been expected to deactivate less than the *p*-iodo-atom.

(iv) Deactivation by *ortho*-substituents is in the order F < I < Cl < Br. The reduction in rate on moving the halogen from the *para*- to the *ortho*-position decreases in the order F > Cl > Br > I, which is consistent with increased importance of the $-I$ effect at the *ortho*-position. It is noteworthy that the importance of the $+T$ effect for the *o*-fluoro-substituent is still sufficient to make this atom less deactivating than a *p*-Br substituent.

In nitration by acetyl nitrate in nitromethane, deactivation by *ortho*-halogens is reported to be in the order I < F < Br < Cl, with iodine several times less deactivating than fluorine.[13]

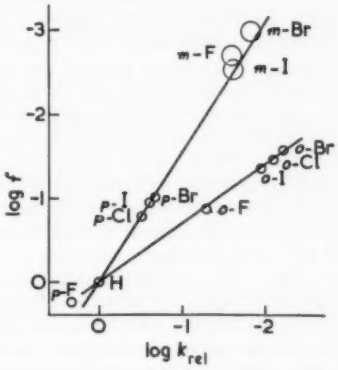
(v) A plot of log *f* for detritiation of $X{\cdot}C_6H_4{\cdot}^3H$ compounds in $CF_3{\cdot}CO_2H(96{\cdot}77)$–$H_2O(0{\cdot}82)$–$HClO_4(2{\cdot}41)$ against log k_{rel} for hydrolysis of $X{\cdot}C_6H_4{\cdot}CMe_2Cl$ compounds in 90% aqueous acetone at 25° [18] (k_{rel} is the rate relative to that of the compound with X = H) is a good straight line for X = H, *p*-Cl, *p*-Br, and *p*-I, but the point for X = *p*-F falls slightly away from this line (see Figure). The approximate points for the *meta*-halogens (see below) lie close to this line. (It follows that except for the deviation by the *p*-F substituent, the effects of the *para*- and *meta*-halogens can be related to the σ^+ constants [19] of the substituents.)

A similar relation applies for the *ortho*-halogens, but the appropriate line lies well away from that for the *meta*- and *para*-substituents (see Figure). Since steric effects of *ortho*-substituents appear to be very small in detritiation,[20] the existence of this relation at first sight implies that steric effects are also negligible for solvolysis of the o-$X{\cdot}C_6H_4{\cdot}CMe_2Cl$ compounds. However, even in absence of steric effects this linear free-energy relation would not be expected, because the extra carbon atom between the substituent and the reaction site in the solvolysis should result in a different balance of $-I$ and $+T$ effects. If, as is usual, the greater deactivation by *ortho*- than by *para*-halogen is attributed mainly to the stronger operation of $-I$ effects to the *ortho*-position, then deactivation by *ortho*- relative to that by *meta*- or *para*-halogens would be expected to be greater in detritiation than in the solvolysis, but the contrary is the case. (Except for fluorine, the halogens deactivate in the hydrolysis more from the *ortho*- than from the *meta*-position.) The low reactivity of the *o*-halogeno-compounds in the hydrolysis has been attributed in part to a steric effect,[18] and it is possible that a chance combination of polar and steric effects results in the linear free-energy relation we have obtained.

The rates of detritiation of m-$X{\cdot}C_6H_4{\cdot}^3H$ compounds could be measured only very roughly because of side-reactions. These are more serious for the *meta*- than for the *ortho*- and *para*-compounds because the detritiation is slower and because the exchange is taking place at the least reactive aromatic position. In the medium containing sulphuric acid, sulphonation was serious, but an approximate value of *f* was obtained for the *m*-Cl compound. The nature of the interference by side reactions in the medium containing perchloric acid is described in the Experimental section; we did not identify these reactions

[14] Kohnstam, *J.*, 1960, 2066.
[15] Ref. 4, p. 240.
[16] de la Mare and Robertson, *J.*, 1948, 100.
[17] de la Mare, *J.*, 1954, 4450.
[18] Brown, Okamoto, and Ham, *J. Amer. Chem. Soc.*, 1957, **79**, 1906.
[19] Brown and Okamoto, *J. Amer. Chem. Soc.*, 1957, **79**, 1913.
[20] Baker and Eaborn, unpublished work.

but we believe that electrophilic substitution of the aromatic compound was involved (possibly in addition to decomposition of the medium) since it was most serious with fluorobenzene, normally the most reactive halogenobenzene towards such substitution. It seemed to be least serious for iodobenzene, and the value of f for *m*-I (see Table) is probably more accurate than those for other *meta*-halogens. The values of f for the *meta*-substituents could be in error by $\pm 100\%$, but there is reasonable agreement between the values for *m*-Cl measured in two media. A safe conclusion is that *meta*- deactivate markedly more



Plot of log f for detritiation of $X \cdot C_6H_4 \cdot {}^3H$ *compounds in* $CF_3 \cdot CO_2H$ (96·77)–H_2O (0·82)–$HClO_4$ (2·41) *at* 55° *against* log k_{rel} *for hydrolysis of* $X \cdot C_6H_4 \cdot CMe_2Cl$ *compounds in* 90% *acetone at* 25°.

than *ortho*- and *para*-halogen, as in other electrophilic aromatic substitutions. It also seems likely that *m*-I deactivates less than the other *meta*-halogens, as in molecular bromination (of halogeno-tri- and -tetra-alkylbenzenes) in nitromethane.[12]

Experimental

General.—A precision-made Vigreux column of low hold-up and equivalent to 18 theoretical plates was used in fractionations.

Stated activities of tritiated aromatic compounds were calculated by assuming maximum use of tritiated water in hydrolysis of Grignard or organolithium reagents, and may be up to five times too large.[2,3]

Measurements of tritium activity were by Eaborn, Taylor, and Matsukawa's method,[21] (with some improvements which will be described later), in which a galvanometer deflection, proportional to the activity, is recorded.

[p-$^3H_1$]*Halogenobenzenes.*—These compounds, of activity *ca.* 4—5 mc/g., were prepared from tritiated water (50—100 mc/g.) and the monomagnesium derivative from *p*-bromofluoro-, *p*-bromochloro-, *p*-dibromo-, or *p*-di-iodo-benzene. In the last case a 1 : 3·5 ether–benzene mixture was used in preparing the Grignard reagent. In this preparation, as in that from *p*-dibromobenzene, [^{3}H]benzene was also obtained, indicating that some dimagnesium derivatives had been formed. The properties and yields of the p-$^3H \cdot C_6H_4 \cdot X$ compounds were as follows: (X =) F, b. p. 85·2°/760 mm., n_D^{20} 1·4658, 70%; Cl, b. p. 132·1°/754 mm., n_D^{20} 1·5245, 75%; Br, b. p. 157·2°/760 mm., n_D^{20} 1·5601, 45%; I, b. p. 188°/760 mm., n_D^{20} 1·6141, 66%.

[m-$^3H_1$]*Halogenobenzenes.*—These were prepared in analogous fashion from *m*-bromofluoro-, *m*-bromochloro-, *m*-bromoiodo-, and *m*-di-iodo-benzene. No benzene was used in the preparation of the Grignard reagent from the last compound. [$^3H_1$]Benzene was formed in large amount (75%) in the preparation starting from *m*-di-iodobenzene, and in small amount in that from *m*-bromoiodobenzene. Properties and yields of the m-$^3H \cdot C_6H_4 \cdot X$ compounds were as follows: (X =) F, b. p. 84—84·5°/750 mm., 58%; Cl, b. p. 132°/750 mm., n_D^{20} 1·5244, 77%; Br, b. p. 156°/760 mm., 53%; I, b. p. 187—188°/760 mm., 11%.

[o-$^3H_1$]*Fluorobenzene.*—Preparation of this compound *via* the Grignard reagent from *o*-bromofluorobenzene was unsatisfactory. The product appeared from rate studies to be

[21] Eaborn, Matsukawa, and Taylor, *Rev. Sci. Instr.*, 1957, **28**, 725.

contaminated with [$^3H_1$]benzene, and, in agreement with this, the material of b. p. 156°, presumed to be mainly unchanged starting material was strongly active and almost certainly contained [$^3H_1$]bromobenzene (b. p. 156°). It thus seems that both the fluorine and bromine enter into the Grignard reaction.

The desired compound was satisfactorily obtained from an organolithium reagent. n-Butyllithium, from butyl bromide (0·08 mole) in ether, was added to a cooled solution of *o*-bromofluorobenzene (0·07 mole) in ether at such a rate that the temperature of the mixture remained below −70°. When addition was complete, tritiated water (0·7 g. of 100 mc/g. activity) was added, followed by an excess of normal water. The usual working-up and fractionation gave [o-$^3H_1$]fluorobenzene (2·0 g., 30%), b. p. 85°, and unchanged *o*-bromofluorobenzene (3·5 g.).

[o-$^3H_1$]*Chlorobenzene*.—The Grignard reagent from *o*-bromochlorobenzene (0·10 mole) and magnesium (0·11 mole) in ether (70 ml.) was treated with tritiated water (1·0 g. of 100 mc/g. activity) followed by an excess of normal water. The usual working-up and fractionation gave [*o*-$^3H_1$]chlorobenzene (5·5 g., 50%), b. p. 131·5—132° (of *ca.* 6 mc/g. activity).

[o-$^3H_1$]*Bromo- and* [o-$^3H_1$]*Iodo-benzene*.—A Grignard reagent was prepared from *o*-bromoiodobenzene (35 g., 0·083 mole) and magnesium (2·02 g., 0·083 mole) in ether (70 ml.), and quickly hydrolysed with tritiated water (2·5 g. of 100 mc/g. activity) followed by an excess of normal water, the mixture being kept below room temperature throughout. After the usual working-up, and addition of 2 ml. each of bromo- and iodo-benzene, fractionation gave benzene (2·0 g.), [*o*-$^3H_1$]bromobenzene (4·2 g.), b. p. 155—156°, and [*o*-$^3H_1$]iodobenzene (4·7 g.), b. p. 187—188°. The calculated activities of the halogenobenzenes were *ca.* 4 mc/g.

Reaction Media.—The trifluoroacetic acid–sulphuric acid medium was prepared by mixing 163·26 g. of 100·0% trifluoroacetic acid and 25·22 g. of 99·7% sulphuric acid, corresponding with a molar-percentage composition of $CF_3{\cdot}CO_2H$ (83·40)–H_2O (1·98)–H_2SO_4 (14·62).

The trifluoroacetic acid–perchloric acid media were made up by weight as follows: (i) 212·29 g. of 100·0% trifluoroacetic acid, 7·112 g. of 72·02 wt.-% aqueous perchloric acid, and 19·56 g. of trifluoroacetic anhydride, corresponding with a molar-percentage composition of $CF_3{\cdot}CO_2H$ (96·772)–H_2O (0·822)–$HClO_4$ (2·406); (ii) 143·74 g. of 100·0% trifluoroacetic acid, 14·39 g. of 72·02 wt.-% perchloric acid, and 30·47 g. of trifluoroacetic anhydride, corresponding with a molar-percentage composition of $CF_3{\cdot}CO_2H$ (89·50)–H_2O (4·55)–$HClO_4$ (5·95).

Rate Measurements.—For detritiation, the general techniques were as previously described, sealed tubes being used for samples in the runs.[1-3] Usually about 0·02—0·07 g. of [$^3H_1$]-halogenobenzene was dissolved in about 7·5 g. of the acid medium. In calculating "equilibrium" deflections at the end of the exchange it was assumed that two aromatic positions were available for tritium in *para*- (one *para* and roughly half of each *ortho*-position), three in *ortho*-, and five in *meta*-halogenobenzenes.

The following sample run refers to [*o*-$^3H_1$]fluorobenzene, 0·0575 g. of which was dissolved in 7·3287 g. of $CF_3{\cdot}CO_2H$ (96·77)–H_2O (0·82)–$HClO_4$ (2·41). Five samples of equal volume were transferred to sealed tubes; a residue of 0·0972 g. of mixture remained, which meant that each sample contained 0·0113 g. of [*o*-$^3H_1$]fluorobenzene. Separate experiments showed that this amount in a 10 ml. extract would give rise to a deflection of 390 mm. at zero time, and thus to 10·5 mm. (D_∞) at equilibrium. In the Table are shown the time of removal of a sample (after the arbitrary zero of the first sample), the deflection, $D_{obs.}$, per 4·365 g. of extract, the deflection D_t calculated for 10·0 ml. of extract, along with the first-order rate-constant, k_{ex}, calculated from the formula $k_{ex}t = 2{\cdot}303 \log [(D_0 - D_\infty)/(D_t - D_\infty)]$.

Time (hr.)	0	0·75	2·45	4·90	7·05
$D_{obs.}$ (mm.)	185·6	167·2	131·8	91·2	68·1
D_t	373·7	336	265·5	184	137
$10^7 k_{ex}$ (sec.$^{-1}$)	—	402	400	419	416

A value of $10^7 k_{ex}$ of 410 sec.$^{-1}$ was derived graphically. In a second experiment a value of 414 sec.$^{-1}$ was obtained.

With [*m*-$^3H_1$]halogenobenzenes accurate measurement of rate constants was prevented by side reactions, which revealed themselves as follows: (i) The reaction mixture progressively darkened. (ii) A scintillation quencher was produced during the reaction, and survived the extraction and decolorization. [This was demonstrated for fluorobenzene by keeping a solution of untritiated fluorobenzene in $CF_3{\cdot}CO_2H$ (89·50)–H_2O (4·55)–$HClO_4$ (5·95) at 55° for 90 hr. and then carrying out the normal extraction and decolorization. When a known weight of the

extract was added to a standard solution of tritiated toluene and liquid scintillator in toluene, the deflection obtained (143 mm.) was lower than that (158 mm.) obtained when the standard solution was diluted with the same weight of toluene containing an appropriate amount of fluorobenzene.] (iii) The initial rate of tritium-loss increased as the initial concentration of [*m*-$^3H_1$]halogenobenzene was lowered, presumably because a side-reaction was removing an increasing proportion of the halogenobenzene. This effect was marked with fluorobenzene and small with bromo- and iodo-benzene. (iv) First-order rate constants fell during a run at normal concentrations of [*m*-$^3H_1$]halogenobenzene, but even with [*m*-$^3H_1$]fluorobenzene this was not as large an effect as might have been expected from observations described under (iii). It seems likely that a fall-off in the rate of loss of tritium was to some extent obscured by the production of a quencher, which would lead to low tritium counts and hence to an apparent increase in the rate of tritium-loss as reaction proceeded.

The effects described under (iii) and (iv) were small for [*m*-$^3H_1$]bromo- and [*m*-$^3H_1$]iodo-, somewhat more marked with [*m*-$^3H_1$]chloro-, and large with [*m*-$^3H_1$]fluoro-benzene. For [*m*-$^3H_1$]iodobenzene the variation in rate-constant from the mean during a run was less than $\pm 10\%$, while the mean rate-constant did not vary by more than 10% over several runs at different initial concentrations, and the value of k_{ex} for this compound is probably accurate to within $\pm 20\%$. For [*m*-$^3H_1$]fluorobenzene the value of k_{ex} could be in error by $\pm 100\%$.

The rates of sulphonation of benzene and *m*-chlorobenzene were measured by spectrophotometric analysis as previously described.[2]

We thank the Department of Scientific and Industrial Research for financial support of this research, and the Research Fund of the Chemical Society for a grant towards the cost of chemicals.

THE UNIVERSITY, LEICESTER. [*Received, December 16th,* 1960.]

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464. *Carbon–Sulphur Fission in Thioethers. Part V.* The Structural Factors Leading to either Carbanion–Sulphenium Fission or Benzoyl Elimination in (α-Benzoylmethylthio)acetic Acids by the Action of Alkalis.*

By YOUSSEF ISKANDER and RASMY TEWFIK.

Thioethers Ph·CO·CXX′·S·CX″X‴·CO_2H readily undergo alkaline hydrolysis with carbanion–sulphenium fission when X″ and X‴ are hydrogen or phenyl, but not when they are methyl, showing the polar rather than the steric effect of these groups to be important.

The Teich–Curtin mechanism, based on proton abstraction from the X″ or X‴ positions, cannot apply when both are phenyl. When X″ and/or X‴ are methyl and X and/or X′ are phenyl, the benzoyl group is eliminated owing to resonance stabilisation of the anion formed; this does not occur when X or X′ is hydrogen or methyl.

THIOETHERS (sulphides), RSZ, are normally very stable towards acids or alkalis, but if R is strongly electron-releasing, the thioether undergoes acidic hydrolysis with carbonium–sulphide fission of the conjugate acid $R-\overset{+}{S}H-Z$, giving ROH and ZSH. On the other hand, when R is electron-withdrawing, the thioether undergoes alkaline fission, giving RH and Z·S·OH,[1] which can be called carbanion–sulphenium fission. Thioethers of the latter type, having the general formula Ph·CO·CXX′·S·CX″X‴·CO_2H were investigated by the authors [2] who found either C–S or CO–C fission according to the natures of the X's.

* Part IV, Iskander and Riad, *J.*, 1961, 223.

[1] Iskander, *J.*, 1948, 1549.
[2] Iskander and Tewfik, *J.*, 1951, 2050.

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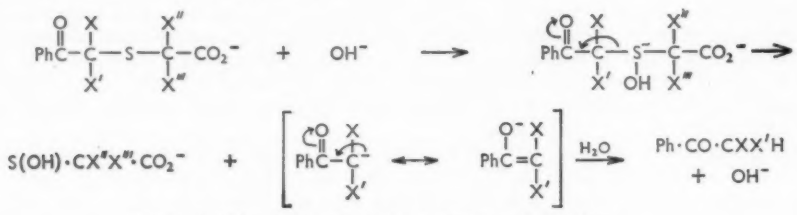
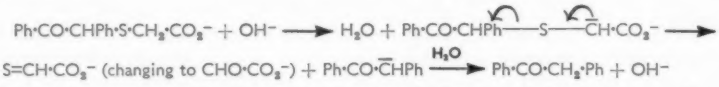
The explanation given,[1,2] based on that of Behaghel and his co-workers,[3,4] was that, as the hydroxyl ion approaches the sulphur atom, made deficient in electrons by the electron-attractive influence of the carbonyl group, the negative charge imposed on the sulphur atom causes separation of the $Ph{\cdot}CO{\cdot}CXX'^-$ anion which receives a hydrogen from a water molecule and regenerates a hydroxyl ion:



When X″, X‴ = H, $S(OH){\cdot}CH_2{\cdot}CO_2^-$ changes to $CHO{\cdot}CO_2^-$.

The methyl groups in the X″ and X‴ positions release electrons to the sulphur atom and thus hinder the approach of the hydroxyl ions.

Teich and Curtin,[5] however, have proposed that the hydroxyl ion abstracts a proton from the X″ and X‴ positions to form an anion which decomposes to the same final products:



They attributed the ease of this proton abstraction to the possibility of expansion of the sulphur valency shell; therefore, in absence of these hydrogen atoms no C–S fission should occur.

The present work was aimed at clarification of three main points: (*a*) Whether our mechanism or Teich and Curtin's is the more probable, by studying cases where both X″ and X‴ are not hydrogen. (*b*) Whether the steric or the polar effects of groups X″ and X‴ cause retardation; they were thus replaced by phenyl which has about the same steric effect but has also $-I \pm T$ effects. (*c*) The influence of methyl and phenyl groups in the X and X′ positions. Table 1 combines results for the present compounds with those previously investigated, and indicates the position(s) of bond fission in the compounds R–S–Z (the standard time of the hydrolysis is 30 min.). The compounds will be discussed in groups.

(I) The (benzoylmethylthio)-acids ($Ph{\cdot}CO{\cdot}CH_2{\cdot}S{\cdot}CX''X'''{\cdot}CO_2H$) (column I). Where X″ and X‴ were phenyl the compound (IE) has undergone 90% of C–S fission, in contrast to the case (ID) where X″ and X‴ were methyl, in which only a trace of C–S fission has occurred. This result indicates: (i) that the absence of hydrogens in X″ and X‴ positions does not stop C–S fission, showing that the Teich–Curtin mechanism is not applicable in this case; (ii) and that the ease of C–S fission of the compound (IE) where X″ and X‴ are phenyl indicates the relative unimportance of steric effects. The phenyl and the methyl groups must have opposite polar effects in these cases. The electron-withdrawing phenyl facilitates approach of hydroxyl ions, while the methyl does not. (iii) The reaction cannot proceed by the S_N1 mechanism, which the methyl groups would have favoured. The " benzoyl " fission did not occur at all in this series of compounds.

(II) The (α-benzoylethylthio)- and (α-benzoylbenzylthio)-acids, $Ph{\cdot}CO{\cdot}CXX'{\cdot}S{\cdot}CX''X'''{\cdot}CO_2H$ (X = H, X′ = Me or Ph). All the (α-benzoylethylthio)-acids (column II) underwent C–S fission, except where X″ and X‴ were both methyl

[3] Behaghel and Schneider, *Ber.*, 1935, **68**, 1588.
[4] Behaghel and Ratz, *Ber.*, 1939, **72**, 1257.
[5] Teich and Curtin, *J. Amer. Chem. Soc.*, 1950, **72**, 2481.

(IID) when no reaction occurred. When they were phenyl (IIE), C–S fission was nearly complete, confirming again that it is the polar nature rather than the steric effect of groups in these positions that controls the reaction. Compound (II'D) underwent a complete " benzoyl fission " with the separation of a substituted benzyl anion.[2]

TABLE 1. *Modes of fission of compounds* RSZ.

	R / –S–Z	I Ph·CO·CH$_2$–	II Ph·CO·CHMe–	II' Ph·CO·CHPh–	III Ph·CO·CMe$_2$–	III' Ph·CO·CPh$_2$–
A	–S·CH$_2$·CO$_2$H	CO—C↓S [6]	CO—C↓S [4]	CO—C↓S [3] 3·5 min.	CO—C↓S	CO↓C↓S [7] 20% 80%
B	–S·CHMe·CO$_2$H	CO—C↓S [2]	CO—C↓S	CO↓C↓S [2] 20% 80%	—	CO↓C—S [2]
C	–S·CHPh·CO$_2$H	CO—C↓S	CO—C↓S	CO—C↓S	—	—
D	–S·CMe$_2$·CO$_2$H	CO—C—S [2] Trace	CO—C—S Unchanged	CO↓C—S [2]	—	CO↓C—S [2]
E	–S·CPh$_2$·CO$_2$H	CO—C↓S 90%	CO—C↓S 90%	CO—C↓S	—	—
F	–S·(CH$_2$)$_2$·CO$_2$H	CO—C↓S [2] 40%	CO—C↓S 30%	CO—C↓S [7] 15% 20 min.	CO—C↓S 30%	CO↓C—S [7]
		X = X' = H	X = H, X' = Me	X = H, X' = Ph	X = X' = Me	X = X' = Ph

(III) The (α-benzoylisopropylthio)- and (α-benzoyldiphenylmethylthio)-acids (X and X' = Me or Ph). When X'' and X''' were hydrogen and X and X' methyls (IIIA), C–S fission was complete. Lengthening the acid chain (IIIF) decreased the fission to 30% but there was no benzoyl fission. The corresponding compounds having phenyl in the X and X' positions undergo " benzoyl " fission to the extent 20% (III'A) and 100% (III'F). This difference is presumably due to the influence of the phenyl groups that stabilise the anion containing two of them. The second phenyl group in the III' series, compared with the series II', favours the benzoyl fission.

EXPERIMENTAL

α-(*Ethoxythiocarbonylthio*)-α-*phenylacetic acid*, Ph·CH(S·CS·OEt)·CO$_2$H, was prepared as described for the analogous isobutyric acids,[8] from α-bromo-α-phenylacetic acid (21·5 g.) and potassium ethyl xanthate (30 g.). It crystallised from carbon tetrachloride in prisms, m. p. 95—96° in almost quantitative yield (Found: C, 51·8; H, 4·8; S, 24·9. $C_{11}H_{12}O_3S_2$ requires C, 51·6; H, 4·7; S, 25·0%).

α-Mercapto-α-phenylacetic acid [9] was obtained as described for α-mercaptoisobutyric acid,[8a] from the above acid. It distilled at 145°/4 mm. (yield 44%). It formed a disulphide, m. p. 218°, identical with an authentic specimen.

α-(*Benzoylmethylthio*)-α-*phenylacetic* (IC) and -α*α-diphenylacetic* (IE), α-(α-*benzoylbenzylthio*)-α-*phenylacetic* (II'C) and -α*α-diphenylacetic* (II'E), and α-*benzylthio*-α-*phenylacetic* (IVC) and -α*α-diphenylacetic* (IVE) *acid* were prepared from the corresponding chloride and the substituted mercaptoacetic acid.

α-(α-*Benzoylethylthio*)-*propionic* (IIB), -α-*methylpropionic* (IID), -*phenylacetic* (IIC), and

[6] Holmberg, *Arkiv Kemi Min. Geol.*, 1936, **12**, *A*, No. 9; *Chem. Zentr.*, 1936, I, 4564.
[7] Schönberg and Iskander, *J.*, 1942, 90.
[8] (*a*) Büilmann, *Annalen*, 1906, **348**, 129; (*b*) Troeger and Volkmer, *J. prakt. Chem.*, 1904, **70**, 488.
[9] Parravano and Tommasi, *Gazzetta*, 1909, **39**, II, 62; Ulpiani and Ciancarelli, *Atti Accad. Lincei*, 1903, **12**, II, 226.

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-diphenylacetic (IIE), β-(α-*benzoylethylthio*)*propionic* (IIF), β-(1-*benzoyl*-1-*methylethylthio*)*propionic* (IIIF), and (1-*benzoyl*-1-*methylethylthio*)*acetic* (IIIA) *acid* were prepared from α-bromopropiophenone or α-bromoisobutyrophenone and the corresponding substituted mercaptoacetic or β-mercaptopropionic acid.

These compounds are recorded in Table 2.

TABLE 2. *Thio-acids.* (*For formulæ see Table* 1.*)

Acid	M. p.	Solvent for crystn.†	Yield (%)	Form	Found (%) C	H	S	Formula	Required (%) C	H	S
IC	120—121°	Benzene	87	Needles	67·3	5·0	11·3	$C_{16}H_{14}O_3S$	67·1	4·9	11·2
IE	169	Toluene	85	Prisms	72·6	4·9	8·8	$C_{22}H_{18}O_3S$	72·9	5·0	8·8
II′C	(a) 137	Benzene–Pet	65	Needles	73·5	5·1	8·6				
	(b) 154		15	Needles	73·1	4·7	8·5	$C_{22}H_{18}O_3S$	72·9	5·0	8·8
II′E	152—153	Toluene–Pet	91	Cubes	76·3	5·1	7·1	$C_{28}H_{22}O_3S$	76·7	5·0	7·3
II′B	101—102	Benzene–Pet	45	Prisms	60·3	6·1	13·7	$C_{12}H_{14}O_3S$	60·5	5·9	13·4
IIF	64	CCl_4	90	Prisms	60·3	5·9	13·1	$C_{12}H_{14}O_3S$	60·5	5·9	13·4
IID	85—87	CCl_4	50	Needles	61·9	6·5	12·5	$C_{12}H_{16}O_3S$	61·9	6·4	12·7
IIC				Oil	(equiv., 302)		10·1	$C_{17}H_{16}O_3S$	(equiv., 300)		10·7
IIE	153—154	Toluene–Pet	56	Plates	73·5	5·4	8·3	$C_{22}H_{20}O_3S$	73·4	5·3	8·5
IIA	77—78	Toluene–Pet	79	Prisms	60·6	5·9	13·4	$C_{12}H_{14}O_3S$	60·6	5·9	13·4
IIIF	84	CCl_4	62	Plates	61·8	6·3	12·4	$C_{12}H_{16}O_3S$	61·9	6·4	12·7
IVC	85—86	Benzene–Pet	87	Needles	70·0	5·5	12·3	$C_{16}H_{14}O_2S$	69·8	5·4	12·4
IVE	185	Benzene	95	Plates	75·4	5·3	9·4	$C_{21}H_{18}O_2S$	75·5	5·4	9·6
VC	118—119	Aq. EtOH	26	Prisms	75·1	5·4	9·8	$C_{21}H_{18}O_2S$	75·5	5·4	9·6
VE	196—198	MeOH	73	Cubes	79·1	5·2	7·3	$C_{27}H_{22}O_2S$	79·0	5·4	7·8

Acid	Hydrolysis products (from 2 g.
IC	a (0·7 g.), b (1·1 g.), H_2S.
IE	a (0·05 g.), t (0·85 g.), u (0·2 g.), H_2S.
II′C	d (1·2 g.), b (0·7 g.), H_2S.
II′E	d (0·9 g.), n (0·1 g.), t (0·2 g.), H_2S.
II′B	p (1·1 g.), H_2S.
IIF	p (0·4 g.), u (1·3 g.), H_2S.
IID	All recovered unchanged.
IIC	p (0·8 g.), b (0·8 g.), H_2S.
IIE	p (0·2 g.), t (0·5 g.), u (0·25 g.), H_2S.
IIA	i (1·6 g.), H_2S.
IIIF	i (0·35 g.), u (1·35 g.).

* In compounds (IV) R = CH_2Ph, and in (V) R = $CHPh_2$ (see Table 1). † Pet = light petroleum (b. p. 50—60°). ‡ Key: (a) Acetophenone; (b) benzoylformic acid; (t) tetraphenylsuccinic acid; (d) deoxybenzoin; (p) propiophenone; (i) isobutyrophenone; (n) benzophenone; (u) unchanged acid.

General Methods of Preparation.—The chloride or bromide (0·02 mole), in ethanol or acetone (40 ml.), was treated with the mercapto-acid (0·02 mole) and sodium hydrogen carbonate (0·04 mole) in water (20 ml.), and the mixture boiled for 15—30 min. Cooling, dilution with water, removal of any turbidity by ether, and acidification gave the required acid.

α-(*Diphenylmethylthio*)-α-*phenylacetic acid* (VC) was prepared by heating a mixture of diphenylmethyl bromide (4·7 g.) and α-mercapto-α-phenylacetic acid (1·7 g.) in the dry state at 110° until no more hydrogen bromide was evolved. Extraction with sodium hydrogen carbonate and acidification gave the acid.

α-(*Diphenylmethylthio*)-αα-*diphenylacetic acid* (VE) was prepared from the chloride (2·9 g.) and α-mercapto-αα-diphenylacetic acid (2·4 g.) by the same method.

Many attempts were carried out to prepare the acids (IIIB, C, D, and E) and (III′C and E) by different methods, but all failed; either the original materials were recovered unchanged or the disulphide of the mercapto-acid used was formed and isolated.

The last four acids (IVC, IVE, VC, and VE) in Table 2 were prepared to be used as references for the products of the " benzoyl " fission in the (II′) and (III′) series. They are all stable to boiling alkali.

General Method of Alkaline Hydrolysis:—The acid (2 g.) in 5% sodium hydroxide (50 ml.) was boiled for 30 min. The liberated acetophenone, propiophenone, or isobutyrophenone was removed by ether and identified as its 2,4-dinitrophenylhydrazone. Results are in Table 2; the acids (IVC, IVE, VC, and VE) were unchanged.

In case of the acid (II′C), the deoxybenzoin (isolated by filtration or ether-extraction) had

m. p. and mixed m. p. 58—60°. With acid (II'E) the oil liberated was found to be a mixture of deoxybenzoin and benzophenone which were separated by fractional crystallisation of their semicarbazones.

The alkaline solution left after hydrolysis usually gave hydrogen sulphide on acidification [except in the cases of the acid (IID) (recovered unchanged), and the acid (IIIF) (the products of hydrolysis do no give hydrogen sulphide on decomposition)]; benzoylformic acid separated in the case of acids (IC, IIC, and II'C), and tetraphenylsuccinic acid in that of acids (IE and IIE). Benzoylformic acid was identified as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 196—197°. Tetraphenylsuccinic acid was purified by washing it with boiling toluene and separated from methanol in scales, m. p. 294° (Found: C, 78·9; H, 5·3%; equiv., 209·6. Calc. for $C_{28}H_{22}O_4$: C, 79·6; H, 5·2%; equiv., 211); the mixed m. p. with an authentic specimen was undepressed; the recorded m. p. [10] 260—262° is incorrect.

The authors acknowledge their indebtedness to Professor D. H. Hey, F.R.S., for his interest and suggestions with respect to the preparation of the manuscripts of this and the following two papers.

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[10] Bickel, *Ber.*, 1889, **22**, 1538.

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465. *Carbon–Sulphur Fission in Thioethers. Part VI.* The Structural Factors Leading to either Carbanion–Sulphenium Fission or α-Proton Extraction in* p-*Nitrophenylmethylthio-acids.*

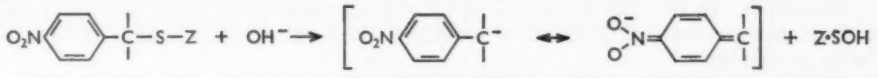
By YOUSSEF ISKANDER and YOUSSEF RIAD.

Alkaline hydrolysis of thioethers p-$O_2N{\cdot}C_6H_4{\cdot}CXX'{\cdot}S{\cdot}CX''X'''{\cdot}CO_2H$ and p-$O_2N{\cdot}C_6H_4{\cdot}CX(S{\cdot}CX''X'''{\cdot}CO_2H)_2$ has been investigated. Carbanion–sulphenium fission occurred with all the compounds in series I, II, and III, and with some of the compounds in series IV and VI (see Table).

The mechanism of the formation of p-azoxybenzaldehyde and p-azoxybenzophenone is discussed.

Whilst p-nitrobenzylthiosalicylic acid is rapidly hydrolysed the oxygen analogue is unchanged.

THIOETHERS (sulphides), p-$O_2N{\cdot}C_6H_4{\cdot}CHX{\cdot}SZ$ and p-$O_2N{\cdot}C_6H_4{\cdot}CX(S{\cdot}CH_2{\cdot}CO_2H)_2$ (X = H or Ph; for Z, cf. Table 1) have been prepared and their sensitivities towards alkalis investigated.[1,2,3,4] Most of these compounds underwent carbanion–sulphenium fission, while the corresponding unnitrated or *m*-nitro-derivatives were recovered unchanged. All the retarding factors, which are increased length of Z or presence of one or two substituted methyl groups in it,[2,4] failed to prevent fission, but in the case of the compound (VA) [3] (cf. Table 1) the second thio-acid group did stop it, although (VIA) underwent fission readily. This difference was attributed to the possibility of *aci*-formation (α-proton-extraction) in (VA), which prevented the C–S fission:



The present work was concerned with the following points: (i) the introduction of further retarding factors in the above structures until the C–S fission is either stopped or

* Part V, preceding paper.

[1] Schönberg and Iskander, *J.*, 1942, 90.
[2] Iskander and Riad, *J.*, 1951, 2054.
[3] Iskander and Salama, *J.*, 1951, 2058.
[4] Iskander and Tewfik, *J.*, 1951, 2050.

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exceeded by the α-proton-extraction, so as to find out the structural conditions favouring the predominance of one process over the other. (ii) An investigation of the mechanism of the transformation of the *p*-nitrobenzyl and *p*-nitrodiphenylmethyl anion in aqueous alkaline solution into the corresponding azoxy-compounds, by trapping any intermediate. (iii) Finding out whether sulphur is essential for this type of fission or if it can be extended to the C–O link.

TABLE 1. *Products of the hydrolysis of the thioethers* $O_2N{\cdot}C_6H_4{\cdot}CXX'{\cdot}SZ$ and $O_2N{\cdot}C_6H_4{\cdot}CX(SZ)_2$ *with boiling* 5% *aqueous sodium hydroxide for* 5 *minutes.*

		A	B	C	D
	Z =	$-CH_2{\cdot}CO_2H$	$-CH_2{\cdot}CH_2{\cdot}CO_2H$	$-CHMe{\cdot}CO_2H$	$-CMe_2{\cdot}CO_2H$
I	$O_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}S-$ ...	azoxy- [1]	azoxy- [1]	azoxy- [2]	azoxy- [2]
II	$O_2N{\cdot}C_6H_4{\cdot}CHPh{\cdot}S-$	azoxy- [3]	azoxy-	azoxy-	azoxy-
III	$(O_2N{\cdot}C_6H_4)_2CH{\cdot}S-$ ...	azoxy- (?)	azoxy- (?)	—	—
IV	$O_2N{\cdot}C_6H_4{\cdot}CPh_2{\cdot}S-$	methane deriv.[1]	unchanged [4]	methane deriv.[4]	unchanged [4]
V	$O_2N{\cdot}C_6H_4{\cdot}CH(S-)_2$ ...	brown-red acid [3]	brown-red acid	brown-red acid	unchanged
VI	$O_2N{\cdot}C_6H_4{\cdot}CPh(S-)_2$ ...	azoxy- [3]	unchanged	—	—

azoxy- = 4,4′-diformylazoxybenzene (from the I series) or 4,4′-dibenzoylazoxybenzene (from the II and VI series).
azoxy- (?) = the azoxy-compounds formed are unidentified.

Table 1 combines the results of the present work with previous work. The unnitrated and the *m*-nitro-compounds are not included since they are all stable to alkalis.

The products of the action of alkali on these compounds were the result of any of the following processes: (*a*) Carbanion–sulphenium fission in which the liberated carbanion has extracted a hydrogen from the solvent to give the methane derivative. This occurs when no α-hydrogen is present (series IV):

$$O_2N{\cdot}C_6H_4{\cdot}CPh_2^- + H_2O \longrightarrow O_2N{\cdot}C_6H_4{\cdot}CHPh_2 + OH^-$$

(*b*) Carbanion–sulphenium fission in which the anion has rearranged to give an azoxy-structure (series I, II, III, and the compound VIA):

$$2(O_2N{\cdot}C_6H_4{\cdot}\bar{C}HX) \longrightarrow X{\cdot}CO{\cdot}C_6H_4{\cdot}NO{=}N{\cdot}C_6H_4{\cdot}COX$$

Compound (VIB), however, is recovered unchanged.

(*c*) Retardation of the C–S fission and, in presence of an α-hydrogen atom (series V), proton-extraction leads to the formation of brown-red acids of unknown structure, still having the nitrogen and the sulphur:

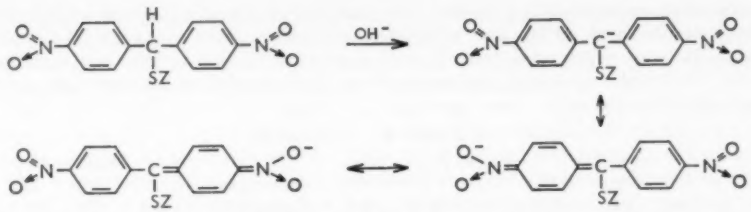
$$O_2NC_6H_4{\cdot}CH(SZ)_2 + OH^- \longrightarrow H_2O + [O_2N{\cdot}C_6H_4{\cdot}\bar{C}(SZ)_2] \longrightarrow \text{Brown-red acid}$$

Compound (VD), however, is recovered unchanged.

Discussion.—(i) In series (I) and (II) of Table 1, the introduction of two methyl groups in Z did not prevent C–S fission, thus providing additional evidence against the Teich–Curtin mechanism.[5]

The compounds (IIIA and B) are interesting because their solutions in sodium hydrogen carbonate are dark red, and in cold sodium hydroxide deep wine-red, which on warming change to brown with the precipitation of yellow products expected to have the azoxy-structure (or a more complicated form of it) similar to those of series (I) and (II). The wine-red colour of the acids in solution is presumably that of the readily formed anion:

[5] Iskander and Tewfik, preceding paper.

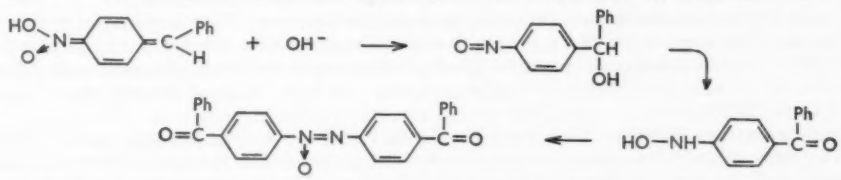


Compounds (VB and C) behaved similar to (VA) previously investigated.[3] They did not undergo C–S fission but changed to brown-red, amorphous, high-melting acids, still containing the nitrogen and sulphur and of unknown structure. Compound (VD), although it has an α-hydrogen atom, was recovered unchanged. It is possible here that the $+I$ effect of the four methyl groups has sufficiently counteracted the labilising influence of the nitro-group on the α-proton.

Compound (VIA) underwent successive C–S fissions,[3] but compound (VIB) was recovered unchanged, thus demonstrating the retarding influence of the length of the acid chain, which could not be detected in series (I, II, and III).

(ii) The azoxy-compounds cannot be formed by direct reduction of the nitro-compounds with sodium sulphide formed in the reaction, since compounds (IVA and C) give sulphide ions but no reduction of the nitro-products occurs, whilst compounds (IB, ID, IIB, and IID) give azoxy-compounds though no sulphide ions are formed. Therefore the azoxy-compounds are probably formed by the rearrangement of the anions resulting from the carbanion–sulphenium fission.

Some support for the mechanism proposed earlier [2] for this transformation was obtained by interrupting the alkaline hydrolysis of the compounds of series (II) before reaction was complete. A compound, m. p. 114—117°, having elementary analysis and properties in agreement with those of 4-nitroso-α-phenylbenzyl alcohol was isolated, though this could not be synthesised. Thus the following reaction sequence may be postulated:



Attempts to prepare the hydroxyamino-compound were not successful, the product being either *p*-aminobenzophenone or 4,4′-dibenzoylazoxybenzene.

(iii) The striking difference between oxygen compounds and their sulphur analogues suggested a comparison of corresponding ethers and thioethers. *p*-Nitrobenzylthiosalicylic acid,[6] when boiled with 5% alkali for 5 min., gave 4,4′-diformylazoxybenzene, whilst the corresponding ether [7] was unchanged by alkali in one hour. The C–S bond fission, therefore, probably occurs by nucleophilic attack by hydroxyl ion on the sulphur atom, which can expand its valency shell whilst oxygen cannot.

Experimental

β-(p-*Nitrodiphenylmethylthio*)*propionic Acid* (IIB).—*p*-Nitrodiphenylmethanol (1 g.) and β-mercaptopropionic acid (0·5 g.) were heated together at 110° while dry hydrogen chloride was passed into the molten mixture for 1·5 hr. Cooling, treatment with sodium hydrogen carbonate solution, removal of turbidity by ether, and acidification gave an *acid* which solidified and separated from benzene–light petroleum in prisms, m. p. 87—89°.

[6] Apitzsch, *Ber.*, 1913, **46**, 3098.
[7] Lyman and Reid, *J. Amer. Chem. Soc.*, 1929, **51**, 1949.

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α-(p-*Nitrodiphenylmethylthio*)-*propionic* (IIC) and -*isobutyric acid* (IID), β-(m-*nitrodiphenylmethylthio*)*propionic acid* (II′B), and α-(m-*nitrodiphenylmethylthio*)-*propionic* (II′C), and -*isobutyric acid* (II′D) were prepared similarly from 1 g. of the alcohol and the equivalent amount (0·5—0·6 g.) of the mercapto-acid, and the products crystallised from benzene–light petroleum; they are recorded in Table 2.

TABLE 2. *Thio-acids.*

		Yield	Found (%)					Required (%)			
Acid	M. p.	(g.)	C	H	N	S	Formula	C	H	N	S
IIB	87—89°	1·2	60·6	5·0	4·2	9·7	$C_{16}H_{15}O_4NS$	60·6	4·7	4·4	10·1
IIC	104—107	1·2	60·9	5·0	4·2	10·3	$C_{16}H_{15}O_4NS$	60·6	4·7	4·4	10·1
IID	174—175	0·25	61·7	5·2	4·5	9·9	$C_{17}H_{17}O_4NS$	61·6	5·1	4·2	9·7
II′B	97—98	1·2	60·7	4·8	4·6	10·6	$C_{16}H_{15}O_4NS$	60·6	4·7	4·4	10·1
II′C	118—120	1·2	60·7	4·8	4·5	10·3	$C_{16}H_{15}O_4NS$	60·6	4·7	4·4	10·1
II′D	153—155	1·3	61·6	5·0	4·4	9·9	$C_{17}H_{17}O_4NS$	61·6	5·1	4·2	9·7

Alkaline Hydrolysis.—The acid (IIB) (3 g.) was boiled with 5% sodium hydroxide solution (75 ml.) for 5 min. The dark brown solution became red with the formation of a yellow-brown sticky mass which solidified (2 g.) and separated from acetic acid in plates, m. p. 200° alone or mixed with authentic 4,4′-dibenzoylazoxybenzene. On acidification of the alkaline filtrate no hydrogen sulphide was evolved but a precipitate was formed which crystallised from hot water in scales, m. p. 155° alone or mixed with authentic ββ′-dithiodipropionic acid. Repetition of the experiment but boiling for 1 min. only, cooling in ice, and dilution with ice-water gave a yellow-brown sticky mass which dissolved completely in warm acetic acid. Precipitation of successive fractions from this solution with water, warming, and then cooling after every addition, gave finally two fractions: (*a*) 4,4′-dibenzoylazoxybenzene; and (*b*) yellow needles, m. p. 114—117° (Found: C, 73·8; H, 5·3; N, 6·4. $C_{13}H_{11}NO_2$ requires C, 73·2; H, 5·2; N, 6·6%). The latter substance gave a positive Liebermann's nitroso-reaction and when boiled with sodium hydroxide solution or acetic acid gave 4,4′-dibenzoylazoxybenzene. It is thought to be 4-*nitroso-α-phenylbenzyl alcohol.*

Alkaline hydrolyses of the acids (IIC and D) gave the above products and differ only in that acidification of the alkaline filtrate of (IIC) gave hydrogen sulphide while that of (IID) gave a precipitate, m. p. 197° alone or mixed with αα′-dithiodi-isobutyric acid but no hydrogen sulphide. The acids (II′B, C, and D) were very stable towards boiling alkali.

pp′-*Dinitrodiphenylmethanol.*—This was prepared by Meerwein–Ponndorf–Verley reduction of 4,4′-dinitrobenzophenone (15 g.) with aluminium isopropoxide (33·6 g.) and propan-2-ol (450 ml.). Acidification gave an *alcohol* (14·5 g.) which separated from toluene in pale yellow needles, m. p. 173—174° (Found: C, 57·0; H, 3·6; N, 10·0. $C_{13}H_{10}O_5N_2$ requires C, 56·9; H, 3·6; N, 10·2%).

pp′-*Dinitrodiphenylmethyl Chloride.*—The alcohol (5·5 g.) and phosphorus pentachloride (4·5 g.) were mixed; hydrogen chloride was evolved in the cold. Heating at 140° for 1 hr., cooling, and pouring into ice-water gave a *chloride* (5 g.) that crystallised from carbon tetrachloride in pale yellow plates, m. p. 111—112° (Found: C, 53·0; H, 3·0; N, 9·1; Cl, 11·8. $C_{13}H_9ClN_2O_4$ requires C, 53·3; H, 3·1; N, 9·5; Cl, 12·1%).

(pp′-*Dinitrodiphenylmethylthio*)*acetic Acid* (IIIA).—The above chloride (5 g.) in alcohol (130 ml.) was treated with a solution of mercaptoacetic acid (2 g.) and sodium hydrogen carbonate (3 g.) in water (20 ml.). Distillation of the alcohol, dilution, filtration from a solid 3·5 g.), and acidification gave the *acid* (1·5 g.) which separated from benzene–light petroleum in pale yellow clusters, m. p. 134—136° (Found: C, 51·3; H, 3·3; N, 8·0; S, 9·0. $C_{15}H_{12}N_2O_6S$ requires C, 51·7; H, 3·4; N, 8·05; S, 9·2%).

The acid (IIIA) (2 g.) was dissolved in 5% sodium hydroxide solution (50 ml.). The deep red solution, on warming, became brown, and after 1 minute's boiling a yellow orange precipitate was formed. After filtration and washing with water, alcohol, and ether, the dry solid (1·5 g.) separated from nitrobenzene–ether as a yellow powder of unknown structure, m. p. >250° (Found: C, 63·9; H, 3·8; N, 8·8%). It is insoluble in molten camphor. Acidification of the alkaline filtrate gave much hydrogen sulphide.

β-(pp′-*Dinitrodiphenylmethylthio*)*propionic Acid* (IIIB).—Prepared in the same way as (IIIA), from the same quantities of chloride and sodium hydrogen carbonate with β-mercaptopropionic acid (2 g.), this acid (1 g.) formed yellow needles, m. p. 148—152° (Found: C, 52·6; H, 4·1; N, 7·7; S, 9·4. $C_{16}H_{14}N_2O_6S$ requires C, 53·0; H, 4·0; N, 8·0; S, 8·8%).

It was hydrolysed in the same way as acid (IIIA). The yellow precipitate (1·5 g.) separated from nitrobenzene–ether as a yellow powder, m. p. >250° (Found: C, 58·3; H, 4·0; N, 20·6%), very different from that obtained from (IIIA) as seen from its analysis. Acidification of the alkaline filtrate gave ββ′-dithiodipropionic acid, m. p. and mixed m. p. 155°.

β- (VB) and α-(p-*Nitrobenzylidenedithio*)*dipropionic* (VC), α-(p-*nitrobenzylidenedithio*)*di*-(α-*methylpropionic*) (VD), β- (V′B) and α-(m-*nitrobenzylidenedithio*)*dipropionic* (V′C), α-(m-*nitrobenzylidenedithio*)*di*-(α-*methylpropionic*) (V′D), β- (V″B) and α-(*benzylidenedithio*)*dipropionic* (V″C), and α-(*benzylidenedithio*)*di*-(α-*methylpropionic acid*) (V″D) were prepared as was (IIB) from the aldehyde (5 g. of benzaldehyde or 7·3 g. of the nitrobenzaldehyde) and the mercapto-acid (10·6 g. of α- or β-mercaptopropionic acid, 11·6 g. α-mercapto-α-methylpropionic acid); they are recorded in Table 3.

TABLE 3. *Dithioacids.*

				Found (%)					Required (%)			
Acid	M. p.	Solvent for crystn.	Yield (g.)	C	H	N	S	Formula	C	H	N	S
VB	120—122°	Aq. EtOH	15·5	45·5	4·5	4·0	18·4	$C_{13}H_{15}O_6NS_2$	45·2	4·4	4·1	18·5
VC	116—118	Benzene	15·5	49·95	4·9	3·7	16·6	$C_{13}H_{15}O_6NS_2,\frac{1}{2}C_6H_6$*	50·0	4·7	3·7	16·7
VD	198—199	C_6H_6–EtOH	8·0	48·7	5·1	3·9	16·5	$C_{15}H_{19}O_6NS_2$	48·3	5·1	3·8	17·2
V′B	147—149	,,	15·5	45·6	4·3	4·1	18·6	$C_{13}H_{15}O_6NS_2$	45·2	4·4	4·1	18·5
V′C	Oil	—	—	44·8	4·3	3·9	18·4	$C_{13}H_{15}O_6NS_2$	45·2	4·4	4·1	18·5
V′D	211—213	C_6H_6–EtOH	8·0	48·1	5·3	3·8	17·1	$C_{15}H_{19}O_6NS_2$	48·3	5·1	3·8	17·2
V″B	87—89	Toluene	13·5	52·0	5·5		21·2	$C_{13}H_{16}O_4S_2$	52·0	5·3		21·3
V″C	145—147	Toluene–Pet	13·5	52·5	5·5		21·1	$C_{13}H_{16}O_4S_2$	52·0	5·3		21·3
V″D	165—166	Toluene	14·5	55·1	6·2		19·6	$C_{15}H_{20}O_4S_2$	54·9	6·1		19·5

* The benzene was not completely removed at 100°/vac.

The acid (VB) (5 g.) dissolved in 5% sodium hydroxide solution (125 ml.) forming a dark red solution. Boiling for 5 min. did not give a precipitate. Acidification precipitated an acid (4·1 g.) and gave a trace of hydrogen sulphide. The precipitated acid was extracted with boiling water from which, on cooling, was precipitated a very small amount of ββ′-dithiodipropionic acid, m. p. 155°. The major product was insoluble in water and most organic solvents, but soluble in alcohol or acetic acid. It was precipitated from alcoholic solution by ether as a brown-red acid, m. p. >250°, insoluble in molten camphor. Its structure is unknown (Found: C, 56·9; H, 4·0; N, 7·8; S, 9·3%).

The acid (VC) was hydrolysed as (VB). No precipitation occurred in the alkaline dark red solution after boiling with the alkali. Acidification gave a little hydrogen sulphide and a brown-red acid which was purified by repeated precipitation from alcohol by ether. It did not melt at 300° (Found: C, 53·2; H, 4·7; N, 5·1; S, 14·9%).

The acid (VD) was recovered after 5 minutes' boiling with alkali. The cold alkaline solution of the acid is light red but, on warming, the red colour deepens and fades again on cooling. The acids (V′B, C, and D) and (V″B, C, and D) also resisted the action of boiling alkali.

β-(*Diphenylmethylenedithio*)*dipropionic Acid* (VI′B).—Benzophenone (6 g.) was heated with β-mercaptopropionic acid (7 g.) at 110° while dry hydrogen chloride was passed in for 4 hr. The *product* (2 g.), extracted as for (IIB) and crystallised from benzene, had m. p. 140—143° (Found: 60·5; H, 5·7; S, 17·1. $C_{19}H_{20}O_4S_2$ requires C, 60·6; H, 5·3; S, 17·0%).

α-(*Diphenylmethylenedithio*)*dipropionic Acid* (VI′C).—The above method failed to give this acid but it was prepared from benzophenone dichloride (3 g.) and α-mercaptopropionic acid (3 g.) at 110° (1 hr.). The acid *product* (0·1 g.), extracted as before and crystallised from toluene, had m. p. 168—170° (Found: C, 60·2; H, 5·4; S, 17·3. $C_{19}H_{20}O_4S_2$ requires C, 60·6; H, 5·3; S, 17·0%).

α-(Diphenylmethylenedithio)di-(α-methylpropionic acid) was not formed on use of the methods for (VI′B and C). The acids (VI′B and VI′C) were very stable towards boiling alkali.

β-(p-*Nitrodiphenylmethylenedithio*)*dipropionic Acid* (VIB).—Prepared from *p*-nitrobenzophenone dichloride (3 g.) and β-mercaptopropionic acid (2·3 g.) as above, this *acid* (2·9 g.) crystallised from benzene–light petroleum and had m. p. 143—145° (Found: C, 54·5; H, 4·8; N, 3·3; S, 15·8. $C_{19}H_{19}NO_6S_2$ requires C, 54·2; H, 4·5; N, 3·3; S, 15·2%).

The acid (1 g.) was dissolved in 5% sodium hydroxide solution (25 ml.). The yellow solution, on warming, changed colour to dark red with the precipitation of a slight amount of a yellow substance containing no sulphur. Acidification of the alkaline filtrate did not give hydrogen sulphide but precipitated the original acid (0·6 g.).

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o-4-*Nitrobenzylthiobenzoic Acid.*—Apitzsch [6] did not identify the product of the action of the alkali on this acid. The acid (5 g.) was boiled for 5 min. in 5% sodium hydroxide solution (125 ml.). A yellow precipitate (0·9 g.) was formed which from benzene formed yellow crystals, m. p. 190° alone or mixed with 4,4′-diformylazoxybenzene. Acidification of the alkaline filtrate gave an orange-red substance which, crystallised from dilute acetic acid, had m. p. 298° alone or mixed with 2,2′-dicarboxydiphenyl disulphide.

o-*Carboxyphenyl* 4-*Nitrobenzyl Ether.*[7]—This ether (1 g.) was boiled with 5% sodium hydroxide solution (25 ml.) for 1 hr. On acidification the acid was recovered.

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466. *Carbon–Sulphur Fission in Thioethers. Part VII.* Kinetics and Mechanism of the Carbanion–Sulphenium Fission in Thioethers.*

By YOUSSEF ISKANDER, YOUSSEF RIAD, and RASMY TEWFIK.

The rates of alkaline hydrolysis of (α-benzoylbenzylthio)acetic acid (I) and β-(4-nitrobenzylthio)propionic acid have been measured. The rate of disappearance of the latter was of the first order, and the reactions are considered to occur by a bimolecular mechanism. A competitive experiment between the above acetic acid and the corresponding 4-nitrobenzylthio-derivative showed that the former reacted much the faster.

IT has been concluded from the qualitative studies in Parts I—VI of this series that alkaline hydrolysis of the thioethers (sulphides) studied proceeds by the nucleophilie attack of the hydroxyl ion on the sulphur atom where the C–S bond is conjugated with a carbonyl or a nitro-group. Support for this conclusion was sought by a quantitative investigation. The rates of the hydrolyses were followed at different concentrations of alkali.

Compounds were employed in which the C–S fission occurs without complications such as " benzoyl " elimination, enolisation, or α-proton-extraction. Examples of the straightforward reactions of this series are those leading to the formation of methane derivatives ($RSZ + H_2O \longrightarrow RH + Z{\cdot}S{\cdot}OH$) or to 4,4′-diformylazoxybenzene formed by rearrangement of the 4-nitrobenzyl anion more rapidly than it extracts a proton from the solvent to give the methane derivative. One compound from each of these two classes was chosen. The first was (α-benzoylbenzylthio)acetic acid (I) which gives deoxybenzoin, in almost a quantitative yield, and carboxymethanesulphenic acid which is transformed in the alkaline medium into glyoxylic acid and sodium sulphide.[1] The rate of this reaction was followed by the determination of the sulphide ion liberated. The second compound chosen was β-(4-nitrobenzylthio)propionic acid (II) which gives a quantitative yield of 4,4′-diformylazoxybenzene (III) and the sulphenic acid which does not decompose to give a sulphide ion in solution but changes to the stable disulphide;[2] no products consuming alkali are formed in the reaction. The corresponding α-(*p*-nitrobenzylthio)acetic acid (IV) was not chosen because it gives a sulphide ion [in the same way as (I)] which reduces the azoxyaldehyde (III) to 4,4′-diformylazobenzene and the product will therefore contain a mixture of the two aldehydes. A competitive experiment, however, was carried with equivalent amounts of acids (I) and (IV), and one equivalent only of the alkali, to examine the difference in the electron-attractive influences of their radicals

From the present and earlier results it is likely that the reactions proceed by a

* Part VI, preceding paper.

[1] Schöberl, *Annalen*, 1933, **507**, 111.
[2] Iskander and Riad, *J.*, 1951, 2054.

bimolecular mechanism. The reactions are specific to alkali and do not occur in aqueous-alcoholic [3] acid. Increase in the concentration of the alkali increases the rate of the reaction. The reaction between the acid (II) and alkali is of the first order (cf. Table), since the alkali concentration remains constant throughout the reaction. Since one molecule only of the acid is involved in the rate-determining stage, this is probably the first one:

$$R{\cdot}SZ + OH^- \xrightarrow{\text{Slow}} R^- + Z{\cdot}S{\cdot}OH \ (\longrightarrow Z{\cdot}SS{\cdot}Z)$$

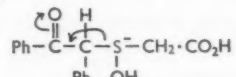
followed by

$$2R^- + 2H_2O \xrightarrow{\text{Fast}} (p\text{-}OHC{\cdot}C_6H_4)_2N_2O + 2OH^-$$

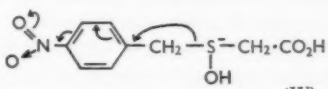
(III)

Experiment (*a*) (cf. the Experimental part) was designed to trap the anion, before rearrangement, with acetaldehyde or acetone but this failed.

The competitive experiment (*b*) shows that, although the nitro-group is more strongly electron-attracting than the carbonyl group, acid (I) undergoes C–S fission faster than acid (IV):



(I)



(IV)

This is probably because conjugation through the benzene ring necessitates a higher energy.

Experiment (*c*) may be explained in the same way: while the acid (I) easily undergoes C–S fission by NaSH or Na_2S, the acid (IV) is not hydrolysed by these reagents.

Experimental

(α-Benzoylbenzylthio)acetic acid (I) (0·01M) was allowed to react with alkali (2, 3, or 4 equiv.) at 30°. The sulphide ion liberated was estimated by a new, simple, accurate procedure: 5 ml. of the reaction mixture were added to 10 ml. 0·01N-silver nitrate acidified with 10 ml. of 0·02N-sulphuric acid, the end of the pipette being dipped under the surface of the solution; the solution was left overnight, then filtered from the silver sulphide with rinsing, and 10 ml. of 0·01N-potassium chloride solution were added; chloride ion was determined by a sensitive electrometric method.[4] The infinity reading never required 10 ml. of 0·01N-silver nitrate. With 4 equiv. of alkali it was only 7·6 ml., with 3 equiv. of alkali it decreased to 6·85 ml.; and with 2 equiv. of alkali it was noticed that as the reaction proceeded the maximum value was 5·55 ml. which began to decrease until the infinity value became 3·65 ml. (these results could not therefore be used in the determination of the order of the reaction). This indicates that the sulphide ions began to act as the nucleophilic reagent. To test this, the reaction was carried out by using disodium sulphide or sodium hydrogen sulphide instead of the alkali:

(i) The acid (I) (1 g.) was treated with aqueous sodium sulphide (prepared from 0·32 g. of sodium in absolute alcohol as usual, by saturating one-half of the sodium ethoxide solution with hydrogen sulphide, adding this to the other half of the ethoxide solution, evaporation of the alcohol, and dissolving the residue in 50 ml. of water). The mixture was boiled on the water-bath for 30 min. The turbid solution, on cooling, precipitated deoxybenzoin (about 0·5 g.). The filtrate, on acidification gave hydrogen sulphide and free sulphur.

(ii) The acid (1 g.) was boiled with aqueous sodium hydrogen sulphide (prepared from 0·16 g. of sodium metal, as above); the same result was obtained.

The second compound β-(*p*-nitrobenzylthio)propionic acid (II) was subjected to the action of two different concentrations of alkali at 30° and at 40°. Every reading was taken from a separate experiment because the *p*-azoxy-aldehyde cannot be suspended homogeneously in a stock reaction mixture. Satisfactory results (see Table) were obtained gravimetrically by using relatively high concentrations to minimise the errors in weighing.

[3] Iskander, *J.*, 1948, 1549.
[4] Best, *J. Agric. Sci.*, 1929, **19**, 533.

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Temp.	Acid (II) (M)	OH– (M)	Reaction (%) at (min.) 10	30	60	120	210	10^3k_1 (min.$^{-1}$)
30°	0·2	0·2	6·8	20·1	40·2	64·2	81·5	8
30	0·2	0·4		43·4	62·8	100		
40	0·2	0·2	19·5	49·5	72·9			22

The activation energy was calculated to be 19 kcal. mole^{-1}.

In all the above experiments duplicate runs were carried out; the values so obtained were almost the same as the recorded ones.

Further Qualitative Experiments.—(*a*) Alkaline hydrolysis of (*p*-nitrobenzylthio)acetic acid (IV) in the presence of a few ml. of acetaldehyde did not proceed as usual,[5] but in the presence of acetone reaction occurred with the precipitation of the *p*-azo-aldehyde.[5]

(*b*) Heating equimolecular amounts of compounds (I) and (IV) with one equivalent only of sodium hydroxide resulted in the precipitation of deoxybenzoin in nearly a quantitative yield, but contaminated with a trace of a brown substance. The filtrate, on acidification, liberated hydrogen sulphide and a brown acid mixture which on extraction with carbon tetrachloride gave some unchanged acid (IV); the brown acid residue which was insoluble in the carbon tetrachloride contained nitrogen and sulphur.

(*c*) Unlike acid (I), the acid (IV) was not hydrolysed with disodium sulphide or sodium hydrogen sulphide but the product was a brown acid containing nitrogen and sulphur.

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[5] Schönberg and Iskander, *J.*, 1942, 90.

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467. 6-*Methoxy*-8-(ω-*piperazin*-1′-*ylalkylamino*)*quinolines*.

By P. A. BARRETT, A. G. CALDWELL, and L. P. WALLS.

Analogues of the pamaquin-type of antimalarial but with a terminal piperazinyl group have been prepared by conventional methods, such as the condensation of 8-amino-6-methoxyquinoline with ω-piperazin-1′-ylalkyl halides. A more versatile method, involving the reduction of side-chains with one or more amide linkages by lithium aluminium hydride, has been devised which affords compounds with various piperazin-1-yl groups attached terminally to alkyl chains of 2—9 carbon atoms. Terminal *N*-substituents with carbonyl groups are simultaneously reduced. 1,2,3,4-Tetrahydroquinolines are occasional by-products. Many of the 6-methoxy-8-ω-piperazin-1′-ylalkylaminoquinolines in which the terminal N atom is basic possess high antimalarial and leishmanicidal properties.

DERIVATIVES of 8-amino-6-methoxyquinoline with a basic side-chain show a range of chemotherapeutic activity.[1] We have now found that similar compounds in which the conventional amino-group has been replaced by 1-piperazinyl (cf. II), hitherto an almost unknown class,[2,3] not only possess very high antimalarial activity but also excel known drugs in their action on *Leishmania donovani* infections in hamsters.[4]

The method of condensation of 8-amino-6-methoxyquinoline with an aminoalkyl halide can be applied to piperazin-1-yl compounds, the most successful modification being that in which the aminoquinoline and the appropriate ω-piperazin-1′-ylalkyl halide (III) dihydrohalide were heated under reflux in propanol. Reaction of the aminoquinoline hydrochloride and piperazin-1-ylalkyl halide gave very similar results although one less molecular equivalent of hydrogen halide was present. The product was readily separated

[1] Schulemann, Schönhöfer, and Wingler, *Klin. Wochenschr.*, 1932, **11**, i, 381; Goble, *J. Parasitol.*, 1949, **35**, 375; Neitz, *Ondersterpoort J. Vet. Res.*, 1957, **27**, 275.
[2] Bachman and Szmant, *J. Amer. Chem. Soc.*, 1946, **68**, 32.
[3] Elderfield *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1525.
[4] Beveridge, Goodwin, and Walls, *Nature*, 1958, **182**, 316.

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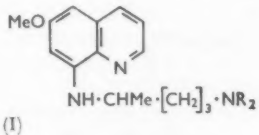
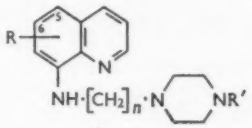
from unchanged aminoquinoline by distillation in a vacuum or by partition between chloroform and a citrate buffer pH 3·85.[3] The piperazin-1-ylalkylaminoquinolines were converted into trihydrochlorides (or dihydrochlorides when the terminal piperazine-N is non-basic, *e.g.*, II; R′ = CO_2Et) which crystallised from alcohols forming orange-coloured



(I)



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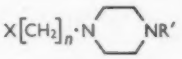

(III)

salts, readily soluble in water and, for the majority, rapidly hydrated on exposure (Table 1). The method was very satisfactory for the preparation of compounds (II) with $n = 3$ [R = 6-OMe, 6-OEt, or 5,6-$(OMe)_2$; R′ = H, Me, Et, CO_2Et, or $CH_2·CH_2·OH$], yields of isolated salt being ~45%. Less satisfactory results were obtained with $n = 6$, and poor yields (*ca.* 10%) with $n = 2$; and in one attempt with $n = 4$ no product was isolated. The scope of the method was evidently limited by the known propensity of aminoalkyl halides of appropriate chain-length to undergo intramolecular quaternisation-cyclisation, thus leading to poor results with tetramethylene and pentamethylene side-chains. Intermolecular quaternisation which is not dependent in the same way on chain-length is probably another yield-reducing complication. Magidson and Strukov [5] claimed to have obtained a small yield of 8-(4-diethylaminobutylamino)-6-methoxyquinoline by the condensation of 8-amino-6-methoxyquinoline with 4-diethylaminobutyl chloride, but no further examples of this condensation have been published. When the tetramethylene chain contains a substituent adjacent to a nitrogen atom, as in plasmoquine (I; R = Et), the products were obtained in rather poor yield as a mixture of position isomers. Pentamethylene compounds have been prepared by this method,[6] but experience has been limited mainly to compounds with terminal secondary amino-groups, in the preparation of which intramolecular alkylation and not quaternisation is the competing side-reaction. With these compounds and indeed with those having other chain-lengths yields vary considerably from compound to compound in a rather unpredictable way.

The condensation of 8-3′-chloropropylamino-6-methoxyquinoline [7] with the appropriate 1-substituted piperazines gave *ca.* 70% yields of compounds (II; $n = 3$, R′ = alkyl or hydroxyalkyl), but where R′ = H reaction at both nitrogen atoms is possible and the yield was only 27%.

Since the leishmanicidal results had pointed to the desirability of testing piperazin-1-yl compounds with tetramethylene, pentamethylene, and longer chains, particularly those with a terminal hydroxyalkyl group, we investigated the reduction of amides of the types (IV)—(VI) by lithium aluminium hydride.[8]

The method with ether as solvent gave 50—60% of crystalline trihydrochloride from amides (IV; R′ = alkyl or alkoxyalkyl) and 30—40% from amides (V). Distillation of the product was not essential but served to remove the small amount of 8-amino-6-methoxyquinoline that is sometimes formed by cleavage. Amides (IV; R′ = H or hydroxyalkyl) and diamides (VI) in tetrahydrofuran usually gave lower yields (25—35%), but exceptionally very high yields resulted, for example, of the crystalline bases (II; $n = 3$, R = 6-OMe, R′ = $[CH_2]_2CHMe·OH$) and (II; $n = 6$, R = OMe, R′ = $CH_2·CHMe·OH$). The rate and course of reductions with lithium aluminium hydride probably depend on the solubility of the various complexes that are formed, and here variation in time and temperature of reaction and reverse addition of the reagents appeared to have only a

[5] Magidson and Strukov, *Arch. Pharm.*, 1933, **271**, 359.
[6] Drake *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1529.
[7] Crum and Robinson, *J.*, 1943, 561.
[8] Micovic and Mihailovic, *J. Org. Chem.*, 1953, **18**, 1190.

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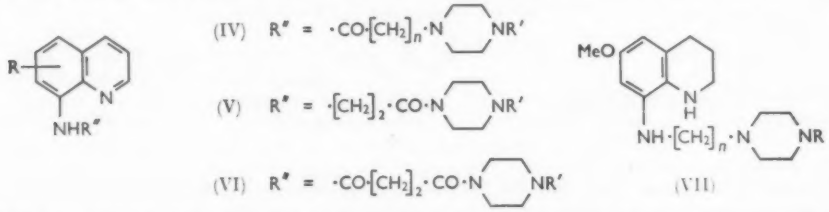
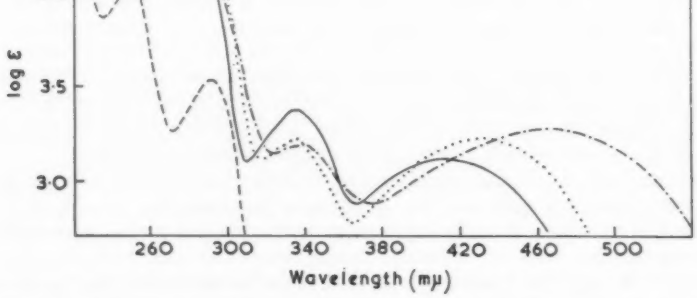
marginal influence. Reduction of the pyridine ring also occurs to a greater or smaller extent and formation of tetrahydroquinolines is certainly one circumstance responsible for the moderate yields sometimes obtained. In two reductions pure tetrahydroquinolines (VII; $n = 4$, R = Et) and (VII; $n = 5$, R = H) were isolated as their trihydrochlorides



which are almost colourless salts distinguished from their quinoline counterparts by absence of absorption at *ca.* 335 and 420 mμ (see Figure). Lithium aluminium hydride is known to reduce quinoline slowly to 1,2-dihydroquinoline, which absorbs at 347 mμ, and

Ultraviolet absorption of: (——) 8-*amino*-6-*methoxyquinoline hydrochloride*; (— · —) 5,6-*dimethoxy*-8-[3-(4-*methylpiperazin*-1-*yl*)*propylamino*]*quinoline trihydrochloride*; (. . .) 6-*methoxy*-8-(5-*piperazin*-1′-*ylpentylamino*)*quinoline trihydrochloride*; *and* (– – –) 1,2,3,4-*tetrahydro*-6-*methoxy*-8-(5-*piperazin*-1′-*ylpentylamino*)*quinoline trihydrochloride.*



may subsequently disproportionate to quinoline and tetrahydroquinoline.[9] Compound (VII; $n = 4$, R = Et) was also obtained by reduction of the corresponding quinoline with excess of sodium in pentyl alcohol, and identity with the lithium aluminium hydride product was established by infrared measurements.

Alternative preparative routes are available for some of the compounds of Table 1. The substituent R′ of the amides (IV—VI) may itself be a group reducible by lithium aluminium hydride. When R′ = CO_2Et the final product is a 6-methoxy-8-(4-methylpiperazin-1-ylalkylamino)quinoline, the urethane group $>N\cdot CO_2Et$ having been reduced to the tertiary amine $>NMe$.[10] In view of the accessibility of 1-ethoxycarbonylpiperazine this variant of the process constitutes a good route to the methylpiperazin-1-yl compounds which are produced thereby in very favourable yield. Likewise amides with R′ = $CH_2\cdot CO_2Et$ and COMe are reduced to 4′-hydroxyethyl- and 4′-ethyl-piperazin-1′-yl compounds respectively. Compounds (II; R′ = CO_2Et) were hydrolysed by aqueous-alcoholic alkali hydroxide with the formation of a base (II; R′ = H). Compounds (II;

[9] Bohlmann, *Chem. Ber.*, 1952, **85**, 390; Neumann, *Annalen*, 1958, **618**, 92.
[10] Dannley, Luken, and Shapiro, *J. Org. Chem.*, 1955, **20**, 92.

R′ = H) undergo reaction at the terminal cyclic NH-group, being converted back into the urethane (II; R′ = CO_2Et) by reaction with ethyl chloroformate, and into hydroxyalkyl compounds (II; R′ = $CH_2{\cdot}CH_2{\cdot}OH$ and $CH_2{\cdot}CHMe{\cdot}OH$) by reaction with alkylene oxides. Similarly reaction with DL-glycidol affords the dihydroxy-compound [II; R′ = $CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}OH$]. The methods have also been applied to the preparation of compounds (II) with R = 6-OEt, 6-OPr, and 5,6-$(OMe)_2$ which are also potent leishmanicides. The 5,6-dimethoxy-compounds form brick-red trihydrochlorides which absorb at longer wavelength than the 6-methoxy-compounds (465 instead of 420 mμ, see Figure).

The amides (IV) (Table 3) were prepared by condensation of the appropriate piperazines with the halogeno-amides (VIII; X = Cl or Br). The latter (Table 2), some of which are known,[11] were prepared by conventional methods. The amides (IV) were usually crystalline for n = 1, 2, 4, and 5 and gums or low-melting solids for n = 3; several formed hydrates. The isolation of amides (IV; R′ = H), which were prepared by condensation of a halide (VIII) and anhydrous piperazine in benzene, was complicated by the simultaneous formation of the diamides (IX) (Table 4) even when an excess of piperazine was used, and by their solubility properties. The amides (IV; n = 3 and 4, R = 6-OMe, R′ = H) are highly soluble in water at room temperature, the former separating on cooling as the crystalline hydrate, which loses water on exposure to air. The lower (n = 2) and higher (n = 5 and 6) amides are less soluble in water at room temperature but otherwise behave similarly. The diamide (IX; n = 4, R = 6-OMe) was reduced by lithium aluminium hydride to the corresponding amine (CH_2 for each CO).

The amides (V) were prepared by condensation of the aminoquinoline with an ω-halogenoacylpiperazine (X), a reaction that is particularly favourable when the terminal nitrogen atom is also non-basic as for R′ = CO_2Et. Similar amides have been described by Neeman.[11a]

The diamides (VI) (Table 5) were prepared by condensation of the 8-aminoquinoline with the succinamic acids (XI), which need not be isolated, in the presence of *NN*′-dicyclohexylcarbodi-imide.[12] The yield of crystalline diamide (VI) varies in some cases with the solvent used. For example, preparation of (VI; R′ = $CH_2{\cdot}CH_2{\cdot}OH$) in pyridine or acetonitrile gave a very low yield, but it was satisfactory in dimethylformamide. In general, conditions giving the highest yields of diamides (VI) were not sought, but the compound (VI; R′ = $CH_2{\cdot}CO_2Et$) was readily obtained in 80% yield. The diamide (VI; R′ = Me) was also obtained by reaction of the quinolylsuccinamic acid (XII) with 4-methylpiperazine in the presence of *NN*′-dicyclohexylcarbodi-imide, but this method was less convenient and appeared to result in the formation of more by-products. Indeed, in an attempt to prepare the diamide (VI; R′ = $CH_2{\cdot}CH_2{\cdot}OH$) by this route, the major product was a compound (XIII) formed by the addition of the acid (XII) to dicyclohexylcarbodi-imide, with little or none of the desired product. This type of by-product has previously been obtained in peptide syntheses by means of *NN*′-dicyclohexylcarbodi-imide.[13]

The 1-alkylpiperazines (Pr^n, Pr^i, Bu^n) required for the preparation of certain of the compounds of Table 1 (method 2) and Table 3 were obtained by the method described by Moore, Boyle, and Thorn [14] for 1-ethylpiperazine, namely, the acid-hydrolysis of the corresponding 4-ethoxycarbonyl compounds.[15] The hydrolyses of the isopropyl [15] and butyl [16] compounds and the products have been described, and the propyl compound has been stated to have been made by the same method.[17] The most satisfactory method of

[11] (*a*) Neeman, *J.*, 1955, 2525; (*b*) Bergmann and Shapiro, *J. Org. Chem.*, 1942, **7**, 419; (*c*) Snyder and Freier, *J. Amer. Chem. Soc.*, 1946, **68**, 2485; (*d*) Hauser, Bloom, Breslow, Adams, Amore, and Weiss, *J. Amer. Chem. Soc.*, 1946, **68**, 1544.
[12] Sheehan and Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067.
[13] Khorana, *Chem. and Ind.*, 1955, 1087.
[14] Moore, Boyle, and Thorn, *J.*, 1929, **39**.
[15] Stewart, Turner, and Denton, *J. Org. Chem.*, 1948, **13**, 134.
[16] Hamlin, Weston, Fischer, and Michaels, *J. Amer. Chem. Soc.*, 1949, **71**, 2732.
[17] Hromatka, Schlager, and Sauter, *Monatsh.*, 1957, **88**, 66.

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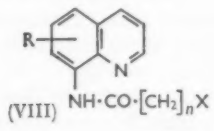
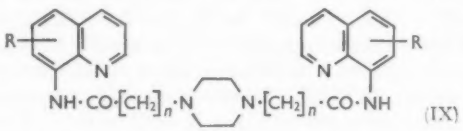
preparing the 1-hydroxy- and 1-alkoxy-alkylpiperazines was reaction of two mol. of 1-ethoxycarbonylpiperazine with the appropriate halogen compound in benzene, followed by hydrolysis of the product by aqueous sodium hydroxide. One product, presumably 1-ethoxycarbonyl-4-3′-hydroxybutylpiperazine, was isolated from the reaction with



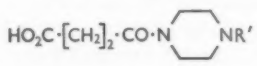
(VIII)



(IX)

1-chloro-3-hydroxybutane.[18] If an oxetane were formed by dehydrochlorination it could conceivably but improbably lead to an isomer. There are two references to *N*-ethoxycarbonylmethylpiperazine [14,19] but neither adequately describes the preparation and properties of this substance. Reaction of piperazine monohydrochloride and ethyl chloroacetate in alcoholic solution furnishes a good yield of the ester with little or no di-ester.

(X)



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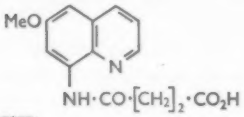
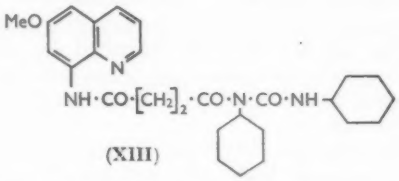


(XII)



(XIII)

Protonation of one nitrogen atom has thus effectively inhibited reaction at that centre with advantageous production of the monosubstituted compound.[20]

1-Bromo-3-chloropropane offers a simple route to the 1-3′-chloropropylpiperazines which is quite satisfactory when one nitrogen atom is non-basic as in 1-ethoxycarbonylpiperazine. With 1-methylpiperazine a yield of 50% can be obtained, but even during distillation at low temperature intramolecular quaternisation is liable to occur with a serious drop in yield. Poor results were obtained with 1-ethylpiperazine, and with 1-2′-hydroxyethylpiperazine the higher boiling point of the product favoured loss by this cause and the method has little preparative value.

The compounds of type (II) were examined for leishmanicidal properties in hamsters by Miss E. Beveridge and Dr. L. G. Goodwin of The Wellcome Laboratories of Tropical Medicine. Activity is usually present when the terminal nitrogen atom of the piperazine ring is basic, and is high when $n = 3$, 4, or 5 and less consistently so when $n = 6$.

Experimental

1-3′-*Hydroxypropylpiperazine*.—1-Ethoxycarbonylpiperazine (63·2 g.) and 1-chloro-3-hydroxypropane (18·9 g.) were heated under reflux in benzene (250 ml.) for 72 hr. The 1-ethoxycarbonylpiperazine hydrochloride (36 g.) that had separated was removed, and the filtrate was evaporated and distilled. 1-*Ethoxycarbonyl-4-3′-hydroxypropylpiperazine* (38 g.) distilled at 122—126°/0·05 mm., n_D^{24} 1·4823 (Found: C, 55·4; H, 8·9; N, 13·2. $C_{10}H_{20}N_2O_3$ requires C, 55·5; H, 9·3; N, 13·0%). This urethane (31 g.) was hydrolysed by heating it under reflux with 2·5N-sodium hydroxide (175 ml.) for 16 hr. An excess of sodium hydroxide

[18] Sondheimer and Woodward, *J. Amer. Chem. Soc.*, 1953, **75**, 5438.
[19] Braker and Christiansen, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1933, **22**, 951.
[20] Cymerman-Craig, Rogers, and Tate, *Austral. J. Chem.*, 1956, **9**, 399.

was added after cooling and the product was extracted with chloroform, dried, and distilled. 1-3′-Hydroxypropylpiperazine (14·2 g.) boiled at 143°/14 mm. and set to a white hygroscopic solid characterised by the dipicrate which crystallised from water in prisms, m. p. 254° (decomp.) in agreement with the literature [21] (Found: C, 37·9; H, 3·9; N, 18·4. Calc. for $C_{19}H_{22}N_8O_{15}$: C, 37·9; H, 3·7; N, 18·6%).

1-3′-*Hydroxybutylpiperazine*.—1-*Ethoxycarbonyl*-4-3′-*hydroxybutylpiperazine*, prepared by the foregoing method, by using 1-chloro-3-hydroxybutane, distilled at 120°/0·1 mm. and had n_D^{24} 1·4800 (Found: C, 56·8; H, 9·5; N, 12·5. $C_{11}H_{22}N_2O_3$ requires C, 57·4; H, 9·6; N, 12·2%). Alkaline hydrolysis converted it into the desired *product*, b. p. 138—139°/14 mm., m. p. 42—43° (Found: C, 60·0; H, 11·4; N, 18·0. $C_8H_{18}N_2O$ requires C, 60·7; H, 11·5; N, 17·8%), giving a *dipicrate* (from aqueous acetone), flat needles, m. p. 234—235° (decomp.) (Found: C, 39·1; H, 3·8; N, 18·2. $C_{20}H_{24}N_8O_{15}$ requires C, 39·0; H, 3·9; N, 18·2%).

1-4′-*Hydroxybutylpiperazine*.—This was prepared by the recorded method [21] except that the alkaline-hydrolysis method described above was advantageously substituted for acid-hydrolysis, the product being obtained in 74% yield, with b. p. 157—159°/13 mm. The *dipicrate*, crystallised from water, had m. p. 234—236° (decomp.) (Found: C, 39·0; H, 3·9; N, 18·1%).

1-2′-*Methoxyethylpiperazine*.—1-*Ethoxycarbonyl*-4-2′-*methoxyethylpiperazine* (26·9 g.) was prepared from 1-ethoxycarbonylpiperazine (50·2 g.) and 2-bromoethyl methyl ether (22·1 g.) by the method described above: it had b. p. 94—96°/0·1 mm., n_D^{25} 1·4702 (Found: C, 55·3; H, 9·0. $C_{10}H_{20}N_2O_3$ requires C, 55·5; H, 9·3%). Alkaline hydrolysis furnished 74% of 1-2′-methoxyethylpiperazine,[20] b. p. 94—95°/14 mm., of which the *dipicrate* (from water) had m. p. 232—233° (decomp.) (Found: C, 38·2; H, 3·7; N, 18·5. $C_{19}H_{22}N_8O_{15}$ requires C, 37·9; H, 3·7; N, 18·6%).

The following were similarly prepared:

1-*Ethoxycarbonyl*-4-2′-*ethoxyethylpiperazine*, b. p. 96°/0·1 mm., n_D^{25} 1·4650 (Found: C, 56·9; H, 9·6; N, 12·3. $C_{11}H_{22}N_2O_3$ requires C, 57·4; H, 9·6; N, 12·2%).

1-2′-*Ethoxyethylpiperazine*, b. p. 104—106°/14 mm., n_D^{23} 1·4677 (Found: N, 17·7. $C_8H_{18}N_2O$ requires N, 17·7%) [*dipicrate* (from water), m. p. 222—223° (decomp.) (Found: C, 38·9; H, 3·8; N, 18·4. $C_{20}H_{24}N_8O_{15}$ requires C, 39·0; H, 3·9; N, 18·2%)].

1-(2,3-*Dihydroxypropyl*)*piperazine*.—1-Ethoxycarbonylpiperazine (31·6 g.) and DL-glycidol (22·2 g.) reacted spontaneously with evolution of heat. When the temperature had subsided the mixture was heated at 100° for 2 hr. and then distilled. 1-(2,3-*Dihydroxypropyl*)-4-*ethoxycarbonylpiperazine* (33·6 g.) boiled at 165°/0·05 mm. (Found: C, 51·3; N, 8·4; N, 11·6. $C_{10}H_{20}N_2O_4$ requires C, 51·7; H, 8·7; N, 12·0%). The *picrate* (from water) had m. p. 145—146·5° (Found: C, 42·2; H, 5·0; N, 15·2. $C_{16}H_{23}N_5O_{11}$ requires C, 41·7; H, 5·0; N, 15·2%). Alkaline hydrolysis of this urethane followed by extraction of the product with chloroform and distillation yielded 1-(2,3-dihydroxypropyl)piperazine which distilled at 128—130°/0·1 mm. (9·5 g.), a viscous hygroscopic liquid which set to low-melting crystals (Found: N, 17·5. Calc. for $C_7H_{16}N_2O_2$: N, 17·5%). The *dipicrate* crystallised from water in prisms, m. p. 236—237° (decomp.) (Found: C, 37·1; H, 3·4; N, 17·9. $C_{19}H_{22}N_8O_{16}$ requires C, 36·9; H, 3·5; N, 18·1%).

1-*Ethoxycarbonylmethylpiperazine*.—To a boiling solution of piperazine hexahydrate (388 g.) and hydrogen chloride (73·0 g.) in alcohol (1 l.) was added gradually ethyl chloroacetate (122·5 g.), and the mixture was boiled for 4 hr. After cooling, piperazine dihydrochloride (166 g.) was filtered off, and the filtrate was evaporated to dryness. The residue was made alkaline with excess of potassium carbonate solution, and the mixture was extracted several times with chloroform. The residue after evaporation of the dried chloroform solution was distilled to give 1-ethoxycarbonylmethylpiperazine [19] (105 g.), b. p. 125—127°/13 mm., n_D^{15} 1·4751. Conveniently equimolar quantities of hexahydrate and dihydrochloride may be used with similar results.

6-*Alkoxy*-8-(ω-*piperazin*-1-*ylalkylamino*)*quinolines* (Table 1).

Method 1. *Condensation of* 8-*Amino*-6-*methoxyquinoline and Piperazin*-1-*ylalkyl Halides* (III).—The halides (III; $n = 2$, R′ = H, X = Cl) [22] and (III; $n = 2$, R′ = Me, X = Cl) [23]

[21] McElvain and Bannister, *J. Amer. Chem. Soc.*, 1954, **76**, 1129.
[22] Hromatka and Engel, *Ber.*, 1943, **76**, 712.
[23] Cymerman-Craig, Harrison, Tate, Thorp, and Ladd, *Austral. J. Chem.*, 1956, **9**, 89.

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TABLE 1. 6-*Alkoxy*-8-(ω-*piperazin*-1′-*ylalkylamino*)*quinolines* (II).

R	R′	*n*	Method	B. p./mm. (or m. p.)	HCl salt: Solvent	HCl salt: M. p.§	Formula	Found (%): C	H	Cl	N	Required (%): C	H	Cl	N
MeO	H	2	1	195—200°/0·005	MeOH	228—229°	$C_{16}H_{22}N_4O,3HCl,0·5H_2O$	47·5	6·3	25·7	13·7	47·5	6·5	26·3	13·8
MeO	Me	2	1, 3*a*	185°/0·01	MeOH	224—225	$C_{17}H_{24}N_4O,3HCl,H_2O$	47·6	6·7	24·9	12·9	47·7	6·8	24·9	13·1
MeO	Et	2	3a	212—214°/0·4	MeOH	230—231	$C_{18}H_{26}N_4O,3HCl,1·5H_2O$	48·2	7·2	23·3	12·6	48·0	7·2	23·6	12·4
MeO	H	3	2, 3a	218—220°/0·2	EtOH	233—234	$C_{17}H_{24}N_4O,3HCl,2H_2O$	46·0	6·8	23·5	12·4	45·8	7·0	23·9	12·6
MeO	Me	3	1, 2, 3a, b, 4	188—191°/0·08	MeOH	227—229	$C_{18}H_{26}N_4O,3HCl,1·5H_2O$ *	48·3	7·4	23·2	12·3	48·0	7·2	23·6	12·4
MeO	Et	3	1	206—212°/0·1	MeOH	235—237	$C_{19}H_{28}N_4O,3HCl,1·5H_2O$	49·0	7·2	23·2	12·3	49·1	7·4	23·0	12·1
MeO	Pr^n	3	2	—	MeOH	235—237	$C_{20}H_{30}N_4O,3HCl,2H_2O$	49·4	7·7	21·8	11·2	49·2	7·6	21·8	11·5
MeO	Bu	3	2	183—186°/0·01	MeOH	242—244	$C_{21}H_{32}N_4O,3HCl,2H_2O$	50·3	7·6	20·9	10·8	50·3	7·8	21·2	11·2
MeO	$[CH_2]_2$·OH	3	1	233—238°/0·05	Aq. EtOH	223—225	$C_{19}H_{28}N_4O_2,3HCl,2H_2O$	46·4	7·0	21·1	11·4	46·4	7·2	21·7	11·4
MeO	$[CH_2]_2$·OH	3	2, 3a	233—237°/0·01	Aq. EtOH	234—236	$C_{20}H_{30}N_4O_2,3HCl,2H_2O$ *	47·8	7·3	21·3	11·1	47·5	7·4	21·1	11·1
MeO	$[CH_2]_4$·OH	3	3a	284—285°/0·15	MeOH	229—230	$C_{21}H_{32}N_4O_2,3HCl,1·5H_2O$	49·3	7·4	20·7	10·6	49·5	7·5	20·9	11·0
MeO	CH_2·CHMe·OH	3	3a	218—220°/0·02	Aq. EtOH	240—242	$C_{20}H_{30}N_4O_2,3HCl$ †	51·0	7·1	22·5	12·3	51·3	7·1	22·8	12·0
MeO	$[CH_2]_2$·CHMe·OH	3	2, 3a	M. p. 109—109·5°	MeOH	241—243	$C_{21}H_{32}N_4O_2,3HCl,2H_2O$ *	48·8	7·8	20·9	10·7	48·7	7·6	20·5	10·8
MeO	$[CH_2]_2$·OMe	3	3a	240—250°/0·1	MeOH	232—234	$C_{20}H_{30}N_4O_2,3HCl,2H_2O$ *	47·6	7·3	20·6	11·1	47·5	7·4	21·1	11·1
MeO	$[CH_2]_2$·OEt	3	3a	218—230°/0·02	Aq. EtOH	226—228	$C_{21}H_{32}N_4O_2,3HCl,H_2O$ *	50·6	7·4	21·4	10·9	50·5	7·5	21·3	11·2
MeO	CO_2Et	3	1	238—243°/0·15	EtOH	194—197	$C_{20}H_{28}N_4O_3,2HCl,2H_2O$	49·7	7·0	14·9	11·9	49·9	7·1	14·7	11·6
MeO	CO·NEt_2	3	2	—	EtOH	192—194	$C_{22}H_{33}N_5O_2,2HCl(2H_2O$ *)†	56·2	7·4	15·1	14·8	56·0	7·4	15·0	14·8
EtO	Me	3	1	—	EtOH	227—229	$C_{19}H_{28}N_4O,3HCl(1·5H_2O$ *)†	51·7	7·1	24·6	13·0	52·1	7·1	24·3	12·8
PrO	Me	3	3a	200—201°/0·05	MeOH	237—239	$C_{20}H_{30}N_4O,3HCl,H_2O$	50·7	7·5	22·4	12·1	51·1	7·5	22·6	11·9
PrO	$[CH_2]_2$·OH	3	3a	M. p. 94—96°	Aq. EtOH	232—234	$C_{21}H_{32}N_4O_2,3HCl,0·5H_2O$ *	51·4	7·4	21·7	11·5	51·4	7·4	21·7	11·4
5,6-$(MeO)_2$	Me	3	1, 3b	—	MeOH	227—228	$C_{19}H_{28}N_4O_2,3HCl$ ‡	50·2	6·8	23·1	12·0	50·3	6·9	23·4	12·3
MeO	H	4	3a	218—224°/0·1	Aq. EtOH	259—260	$C_{18}H_{26}N_4O,3HCl,2·5H_2O$	46·5	7·5	22·5	11·9	46·1	7·3	22·7	11·9
MeO	Me	4	3a, b, 5	216—220°/0·01	Aq. EtOH	246—248	$C_{19}H_{28}N_4O,3HCl$ †	52·1	7·1	24·1	12·9	52·1	7·1	24·3	12·8
MeO	Pr^i	4	3a	—	MeOH	227—229	$C_{21}H_{32}N_4O,3HCl$ †	54·3	7·7	23·2	12·1	54·1	7·6	22·8	12·0
MeO	$[CH_2]_2$·OH	4	3a, b, 5	236—238°/0·02	MeOH	227—228	$C_{20}H_{30}N_4O_2,3HCl(2H_2O$ *)†	50·9	6·9	22·6	12·0	51·3	7·1	22·8	12·0
MeO	$[CH_2]_2$·CHMe·OH	4	3a	232—239°/0·05	Aq. EtOH	229—231	$C_{22}H_{34}N_4O_2,3HCl,2·5H_2O$ *	49·1	7·9	19·6	10·3	48·9	7·8	19·7	10·4
MeO	CH_2·CH(OH)·CH_2·OH	4	3a	—	MeOH	218—220	$C_{21}H_{32}N_4O_3,3HCl,3·5H_2O$ *	45·1	7·1	18·7	9·8	45·0	7·5	19·0	10·0
5,6-$(MeO)_2$	H	4	3a	—	Aq. EtOH	237—238	$C_{19}H_{28}N_4O_2,3HCl$	50·5	7·2	23·1	12·3	50·3	6·9	23·4	12·3
5,6-$(MeO)_2$	Me	4	5	194—198°/0·02	EtOH	218	$C_{20}H_{30}N_4O_2,3HCl,2H_2O$ *	—	—	21·1	11·0	—	—	21·1	11·1
MeO	H	5	3a	244—250°/0·1	Aq. EtOH	265	$C_{19}H_{28}N_4O,3HCl,H_2O$	50·0	7·4	22·6	—	50·0	7·3	23·4	—
MeO	Me	5	3a, b	210—214°/0·01	MeOH	236—238	$C_{20}H_{30}N_4O,3HCl,2·5H_2O$	48·1	7·5	21·4	11·3	48·3	7·7	21·5	11·3
MeO	Pr^i	5	3a	216—219°/0·01	EtOH	226—228	$C_{22}H_{34}N_4O,3HCl(H_2O$ *) †	55·2	7·7	22·0	12·0	55·1	7·8	22·2	11·7
MeO	$[CH_2]_2$·OH	5	3a	262—264°/0·1	MeOH	219—221	$C_{21}H_{32}N_4O_2,3HCl(2H_2O$ *) †	52·6	7·2	22·1	11·6	52·3	7·3	22·1	11·6
EtO	Me	5	3a	M. p. 58·5—60°	MeOH	237—238	$C_{21}H_{32}N_4O,3HCl$ †	53·9	7·5	23·0	11·9	54·1	7·6	22·8	12·0
EtO	$[CH_2]_2$·OH	5	3a	244—252°/0·08	MeOH	228—230	$C_{22}H_{34}N_4O_2,3HCl,0·5H_2O$ *	52·2	7·0	21·1	11·2	52·3	7·6	21·1	11·1
MeO	H	6	1, 3a	248—254°/0·1	EtOH	*ca.* 156—158	$C_{20}H_{30}N_4O,3HCl,2H_2O$	48·7	7·6	22·1	11·4	49·2	7·6	21·8	11·5
MeO	Me	6	1	218—224°/0·05	EtOH	232—233	$C_{21}H_{32}N_4O,3HCl,1·5H_2O$	51·2	7·6	21·9	11·5	51·2	7·8	21·6	11·4
MeO	Pr^i	6	3a	250—254°/0·03	MeOH	229—231	$C_{23}H_{36}N_4O,3HCl,H_2O$ *	53·9	7·9	20·7	10·8	53·9	8·1	20·8	10·9
MeO	$[CH_2]_2$·OH	6	3a	270—278°/0·15	Aq. EtOH	219—221	$C_{22}H_{34}N_4O_2,3HCl,2H_2O$	49·6	7·6	19·8	10·4	49·7	7·8	20·0	10·5
MeO	CH_2·CHMe·OH	6	3a	M. p. 109·5°	MeOH	213—215 (maleate)	$C_{23}H_{36}N_4O_2,3HCl(2H_2O$ *) †	54·1	7·3	20·9	10·8	54·2	7·7	20·9	11·0
EtO	Me	6	1	214—222°/0·01	Aq. EtOH	166—167	$C_{23}H_{34}N_4O,2C_4H_4O_4$	59·7	7·0	—	9·3	59·8	7·0	—	9·3
MeO	H	7	3a	242—244°/0·2	Aq. EtOH	227—228	$C_{21}H_{32}N_4O,3HCl,1·5H_2O$	51·5	7·7	22·3	11·5	51·2	7·7	21·6	11·4
MeO	Me	7	3a	206—208°/0·01	EtOH	232	$C_{22}H_{34}N_4O,3HCl$ †	—	—	22·0	11·5	—	—	22·2	11·7
MeO	Pr^i	7	3a	228—230°/0·01	EtOH	230	$C_{24}H_{38}N_4O,3HCl,2H_2O$ *	—	—	19·0	10·2	—	—	19·5	10·3
MeO	$[CH_2]_2$·OH	7	3a	244—248°/0·01	EtOH	205—207	$C_{23}H_{36}N_4O_2,3HCl,2H_2O$ *	—	—	19·9	10·2	—	—	19·5	10·3
MeO	Me	8	3a	212—216°/0·01	Pr^{i}OH	225	$C_{23}H_{36}N_4O,3HCl$ †	—	—	21·0	11·3	—	—	21·5	11·3
MeO	Me	9	3a	217—218°/0·01	Pr^{i}OH	220	$C_{24}H_{38}N_4O,3HCl$ †	—	—	20·5	11·1	—	—	20·9	11·0

* " Loss " was determined and supported the formula stated. † These compounds were analysed after drying. ‡ Found: MeO, 14·1. Required: MeO, 13·7%.
§ With decomp.

* " Loss " was determined and supported the formula stated. † These compounds were analysed after drying. ‡ Found: MeO, 14·1. Required: MeO, 13·7%.
§ With decomp.

TABLE 2. *Quinoline halogeno-amides* (VIII).

R	X	*n*	Solvent for crystn.	M. p.	Formula	Found (%) C	H	Hal	N	Required (%) C	H	Hal	N
5,6-(MeO)$_2$	Cl	2	EtOH	119°	$C_{14}H_{15}ClN_2O_3$ ...	—	—	11·9	9·5	—	—	12·0	9·5
6-PrO	Cl	2	EtOH	124—126	$C_{15}H_{17}ClN_2O_2$ ...	61·8	5·9	12·1	9·6	61·6	5·9	12·1	9·6
6-MeO	Cl	3	Aq. EtOH	69—71	$C_{14}H_{15}ClN_2O_2$ ...	60·7	5·4	12·8	9·9	60·3	5·4	12·7	10·1
5,6-(MeO)$_2$	Cl	4	Aq. EtOH	57—58 *	$C_{15}H_{17}ClN_2O_3$ ...	58·1	5·8	12·2	—	58·4	5·5	11·5	—
6-MeO	Br	4	EtOH	115—116·5	$C_{15}H_{17}BrN_2O_2$	53·4	5·0	23·5	8·4	53·4	5·1	23·7	8·3
6-EtO	Br	4	Acetone	99—100	$C_{16}H_{19}BrN_2O_2$	54·9	5·2	22·8	7·8	54·7	5·4	22·8	8·0
6-MeO	Br	5	EtOH	71·5—73	$C_{16}H_{19}BrN_2O_2$	—	—	22·8	8·0	—	—	22·8	8·0
6-MeO	Br †	6	MeOH	109—111	$C_{17}H_{21}BrN_2O_2$	—	—	21·4	7·8	—	—	21·9	7·7
6-MeO	Br †	7	MeOH	63—65	$C_{18}H_{23}BrN_2O_2$ ...	57·3	6·2	20·8	7·4	57·0	6·1	21·1	7·4
6-MeO	Cl †	8	MeOH	97—99	$C_{19}H_{25}ClN_2O_2$ ...	65·6	7·0	10·3	8·2	65·4	7·2	10·2	8·0

* Crystallises as a hydrate which gives m. p. and analytical figures after dehydration. † The acid chlorides were obtained by heating the corresponding acids with thionyl chloride: 7-bromoheptanoyl, b. p. 134°/11 mm.; 8-bromo-octanoyl, b. p. 136°/9 mm.; 9-chlorononanoyl, b. p. 134°/10 mm.

TABLE 3. *6-Alkoxy-8-(ω-piperazin-1′-ylacylamino)quinolines* (IV).

R	R′	*n*	Method	Derivative	Solvent for crystn.‡	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
MeO	Me	1	A	—	MeOH	113°	$C_{17}H_{22}N_4O_2$	65·2	6·9	17·5	64·9	7·0	17·8
MeO	Et	1	A	—	Pet	103·5	$C_{18}H_{24}N_4O_2$	66·1	7·3	17·1	65·8	7·4	17·1
MeO	H	2	D	—	EtOAc	130	$C_{17}H_{22}N_4O_2$	64·9	6·6	17·7	64·9	7·0	17·8
MeO	Me	2	A	—	EtOAc	95—96 *	$C_{18}H_{24}N_4O_2$	66·1	7·3	16·9	65·8	7·4	17·1
MeO	$[CH_2]_2$·OH	2	A	—	C_6H_6–Ch	132—133	$C_{20}H_{28}N_4O_3$	64·6	7·5	15·0	64·5	7·6	15·0
MeO	$[CH_2]_4$·OH	2	A	—	EtOAc	123—124	$C_{21}H_{30}N_4O_3$	65·2	7·7	14·2	65·3	7·8	14·5
MeO	CH_2·CHMe·OH	2	A	—	Ch	117·5—118·5	$C_{20}H_{28}N_4O_3$	64·4	7·6	15·1	64·5	7·6	15·0
MeO	$[CH_2]_2$·CHMe·OH	2	A	—	EtOH	160—162	$C_{21}H_{30}N_4O_3$	65·3	7·5	14·3	65·3	7·8	14·5
MeO	$[CH_2]_2$·OMe	2	A	Di-(H maleate)	EtOH	175	$C_{20}H_{28}N_4O_3,2C_4H_4O_4$	55·6	6·0	9·2	55·6	6·0	9·2
MeO	$[CH_2]_2$·OEt	2	A	—	Et_2O–Pet	82—83	$C_{21}H_{30}N_4O_3$	65·3	7·7	14·3	65·3	7·8	14·5
PrO	Me	2	A	—	Ch	101—102	$C_{20}H_{28}N_4O_3$	67·3	7·8	15·7	67·4	7·9	15·7
PrO	$[CH_2]_2$·OH	2	A	—	EtOAc	126—127	$C_{21}H_{30}N_4O_3$	65·5	7·6	14·7	65·3	7·8	14·5
5,6-$(MeO)_2$	CO_2Et	2	B	—	Ch	121—122	$C_{21}H_{28}N_4O_5$	60·3	6·7	13·3	60·6	6·8	13·4
MeO	H	3	D	—	Pet	113 *	$C_{18}H_{24}N_4O_2$	66·1	7·2	16·9	65·8	7·4	17·1
MeO	Me	3	B	Di-(H maleate)	MeOH	190—191	$C_{19}H_{26}N_4O_2,2C_4H_4O_4$	56·1	6·0	9·5	56·4	6·0	9·7
MeO	CO_2Et	3	B	—	Pet	76—77	$C_{21}H_{28}N_4O_4$	62·9	6·7	14·0	63·0	7·0	14·0
MeO	Pr^i	3	B	Di-(H maleate)	MeOH	186—187	$C_{21}H_{30}N_4O_2,2C_4H_4O_4$	57·7	6·0	9·1	57·8	6·4	9·3
MeO	$[CH_2]_2$·OH	3	A, B, C	Di-(H maleate)	MeOH	166—167	$C_{20}H_{28}N_4O_3,2C_4H_4O_4$	55·9	6·0	9·1	55·6	6·0	9·2
MeO	CH_2·CO_2Et	3	C	Di-(H maleate)	EtOH	151	$C_{23}H_{30}N_4O_4,2C_4H_4O_4$	55·2	6·1	8·7	55·7	5·9	8·7
MeO	$[CH_2]_2$·CHMe·OH	3	B	Di-(H maleate)	EtOH	181·5	$C_{23}H_{32}N_4O_3,2C_4H_4O_4$	56·9	6·5	8·9	57·0	6·4	8·9
MeO	CH_2·CH(OH)·CH_2·OH	3	A	Dipicrate	H_2O	230° (decomp.)	$C_{21}H_{30}N_4O_4,2C_6H_3N_3O_7$	45·8	4·2	15·8	46·0	4·3	16·3
5,6-$(MeO)_2$	H	3	D	—	EtOAc	105—106	$C_{19}H_{26}N_4O_3$	63·9	7·0	15·5	63·7	7·3	15·6
MeO	H	4	D	—	Pet	104—106	$C_{19}H_{26}N_4O_2$	66·6	7·5	16·4	66·6	7·6	16·4
MeO	Me	4	C	—	Ch	81·5—83·5	$C_{20}H_{28}N_4O_2$	67·1	7·9	15·7	67·4	7·9	15·7
MeO	CO_2Et	4	A	—	EtOAc	113—114	$C_{22}H_{30}N_4O_4$	63·6	7·2	13·3	63·7	7·3	13·5
MeO	Pr^i	4	B	Di-(H maleate)	EtOH	180·5	$C_{22}H_{32}N_4O_2,2C_4H_4O_4$	58·3	6·4	8·9	58·4	6·5	9·1
MeO	$[CH_2]_2$·OH	4	B	—	C_6H_6	70—71	$C_{21}H_{30}N_4O_3$	65·4	7·5	14·2	65·3	7·8	14·5
EtO	Me	4	B	Di-(H maleate)	EtOH	184	$C_{21}H_{30}N_4O_2,2C_4H_4O_4$	57·5	6·6	9·1	57·8	6·4	9·3
EtO	$[CH_2]_2$·OH	4	A	Di-(H maleate)	EtOH	151·5	$C_{22}H_{32}N_4O_3,2C_4H_4O_4$	57·3	6·2	8·8	57·0	6·4	8·9
MeO	H	5	D	—	Ether	102	$C_{20}H_{28}N_4O_2$	67·6	7·6	15·6	67·4	7·9	15·7
MeO	Pr^i	5	B	Di-(H maleate)	EtOH	181—182	$C_{22}H_{34}N_4O_2,2C_4H_4O_4$	58·9	6·8	8·8	59·0	6·7	8·9
MeO	$[CH_2]_2$·OH	5	B	—	C_6H_6	97·5—98·5	$C_{22}H_{32}N_4O_3$	66·0	7·7	13·8	66·0	8·0	14·0
MeO	CH_2·CHMe·OH	5	B	—	C_6H_6	126—127·5	$C_{22}H_{34}N_4O_3$	66·8	8·4	13·5	66·6	8·3	13·5
MeO	H	6	D	—	Ether	98	$C_{21}H_{30}N_4O_2$	67·9	7·9	14·5	68·1	8·2	15·1
MeO	Me	6	B	—	Ether	81—82	$C_{23}H_{32}N_4O_2$	68·6	8·2	14·2	68·7	8·4	14·6
MeO	Pr^i	6	B	—	Pet	65—66	$C_{24}H_{36}N_4O_2$	70·3	8·9	13·6	69·9	8·8	13·6
MeO	$[CH_2]_2$·OH	6	B	Di-(HCl)		193—195	$C_{23}H_{34}N_4O_2,2HCl$	—	—	11·3	—	—	11·5
MeO	Me	7	B	—	Pet	64—66	$C_{23}H_{34}N_4O_2$	69·6	8·2	14·1	69·3	8·6	14·1
MeO	Me	8	B	—	Pet	67—79	$C_{24}H_{36}N_4O_2$	70·1	8·9	13·8	69·9	8·8	13·6

* M. p. after crystalline hydrate had lost water on exposure. † The base crystallised from water as a hydrate which lost water on exposure and became gummy. ‡ Pet = light petroleum (b. p. 60—80°); Ch = cyclohexane.

were prepared by the recorded methods. The preparation of the other halides and the condensation with the aminoquinoline were as follows:

1-3′-*Chloropropyl*-4-*methylpiperazine* (III; $n = 3$, R′ = Me, X = Cl). 1-Methylpiperazine (70 g.), 1-chloro-3-bromopropane (52·5 g.), and dry benzene were heated under reflux for 4 hr. After cooling, the benzene solution was separated from solid and extracted with 3N-hydrochloric acid (3 × 75 ml.). The extract was made strongly alkaline with solid sodium hydroxide, and the liberated *base* was removed with ether, dried, and distilled at 98—100°/8 mm. (28·5 g.) (Found: Cl, 19·5; N, 16·3. $C_8H_{17}ClN_2$ requires Cl, 20·1; N, 15·9%). The dihydrochloride has been described.[24]

1-3′-*Chloropropyl*-4-*ethoxycarbonylpiperazine*, b. p. 109°/0·1 mm. (Found: C, 51·1; H, 8·0; Cl, 15·1; N, 12·0. $C_{10}H_{19}ClN_2O_2$ requires C, 51·2; H, 8·2; Cl, 15·1; N, 11·9%), and 1-3′-*chloropropyl*-4-2′-*hydroxyethylpiperazine*, b. p. 95—96°/0·01 mm. (Found: C, 52·0; H, 9·2; Cl, 17·4; N, 13·6. $C_9H_{19}ClN_2O$ requires C, 52·3; H, 9·3; Cl, 17·2; N, 13·6%), were similarly prepared, the yield of the latter being very poor.

TABLE 4. *The bisquinoline amides* (IX).

R	n	Solvent for crystn.	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
6-MeO	2	2-Ethoxyethanol	230°	$C_{20}H_{24}N_6O_4$	66·1	6·1	15·3	66·4	6·3	15·5
6-MeO	3	EtOH	144—146	$C_{22}H_{28}N_6O_4$	67·3	6·6	14·6	67·4	6·7	14·7
5,6-$(MeO)_2$	3	Pet	134—135	$C_{24}H_{32}N_6O_6$	64·2	6·9	12·8	64·8	6·7	13·3
6-MeO	4	EtOH	149—150	$C_{24}H_{32}N_6O_4$	67·8	7·0	14·1	68·3	7·0	14·0
6-MeO	5	EtOH	168	$C_{26}H_{36}N_6O_4$	68·8	7·2	—	69·0	7·4	—

TABLE 5. *The diamides* (VI).

R	R′	Solvent for prep.	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
6-MeO	Me *	$CHCl_3$	164—165°	$C_{19}H_{24}N_4O_2$	64·0	6·8	15·8	64·0	6·8	15·7
6-MeO	CO_2Et *	$CHCl_3$	137—138	$C_{21}H_{26}N_4O_4$	60·9	6·3	13·6	60·9	6·3	13·5
6-MeO	$[CH_2]_2$·OH †	H·CO·NMe_2	143—145	$C_{20}H_{26}N_4O_4$	62·1	7·2	14·1	62·2	6·8	14·5
6-MeO	CH_2·CO_2Et †	$CHCl_3$	92—93	$C_{22}H_{28}N_4O_5$	61·3	6·5	12·7	61·7	6·6	12·7
5,6-$(MeO)_2$	CO_2Et	$CHCl_3$	155—156	$C_{22}H_{28}N_4O_6$	59·6	6·3	12·4	59·4	6·3	12·6

*† These diamides on reduction gave the same product: Table 1, * R′ = Me, † R′ = $[CH_2]_2$·OH)

By essentially the methods of Cowan and Marvel [25] the following were obtained: 1-*Ethyl*-4-3′-*phenoxypropylpiperazine*, b. p. 135—137°/0·4 mm. (Found: C, 72·7; H, 9·7; N, 11·2. $C_{15}H_{24}N_2O$ requires C, 72·5; H, 9·7; N, 11·3%), 1-3′-*bromopropyl*-4-*ethylpiperazine dihydrobromide*, colourless plates (from ethanol), m. p. 234° (effervescence) (Found: C, 27·4; H, 5·3; Br, 60·3; N, 7·1. $C_9H_{21}Br_3N_2$ requires C, 27·2; H, 5·3; Br, 60·4; N, 7·1%), 1-6′-*methoxyhexyl*-4-*methylpiperazine*, b. p. 122—124°/4·5 mm., n_D^{22} 1·4659 (Found: C, 67·1; H, 12·5; N, 13·0. $C_{12}H_{26}N_2O$ requires C, 67·2; H, 12·2; N, 13·0%), and 1-6′-*bromohexyl*-4-*methylpiperazine dihydrobromide*, soft needles (from ethanol), m. p. 242—244° (Found: C, 31·1; H, 5·8; Br, 56·2; N, 6·7. $C_{11}H_{25}Br_3N_2$ requires C, 31·1; H, 5·9; Br, 56·4; N, 6·6%).

6-*Methoxy*-8-[3-(4-*methylpiperazin*-1-*yl*)*propylamino*]*quinoline trihydrochloride*. 8-Amino-6-methoxyquinoline hydrochloride (25·6 g.), 1-3′-chloropropyl-4-methylpiperazine (20·2 g.), and propan-1-ol (120 ml.) were heated under reflux for 72 hr. An excess of aqueous sodium hydroxide was added and the basic product was extracted with ether. After evaporation of ether the residue was shaken with chloroform–citrate buffer (pH 3·85) (30 ml. of each). The chloroform layer contained unchanged aminoquinoline. The citrate layer was made alkaline and the basic product was isolated with ether and dissolved in 3 equivalents of N-hydrochloric acid. The solution was evaporated to dryness under reduced pressure and the residue was crystallised twice from methanol, forming orange needles which rapidly became hydrated (22·5 g.).

6-*Ethoxy*-8-[6-(4-*methylpiperazin*-1-*yl*)*hexylamino*]*quinoline trihydrochloride*. 8-Amino-6-ethoxyquinoline (36 g., 3 equiv.), 1-6′-bromohexyl-4-methylpiperazine dihydrobromide (22·2 g., 1 equiv.) and propan-1-ol (20 ml.) were heated under reflux for 72 hr. The base was liberated

[24] Hromatka, Grass, and Sauter, *Monatsh.*, 1956, **87**, 706.
[25] Cowan and Marvel, *J. Amer. Chem. Soc.*, 1936, **58**, 1537.

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by alkali, isolated with ether, and distilled. A fraction (17·2 g.) boiling at 120—135°/0·01 mm. consisted of 8-amino-6-ethoxyquinoline, and the product (7 g.) distilled at 214—222°/0·01 mm. The *dimaleate* (Table 1) was obtained by reaction of the constituents in hot ethyl acetate. The pale yellow crystals were recrystallised from aqueous alcohol (10% water) forming cream-coloured clumps of needles, m. p. 166—167° with effervescence.

Method 2. *Condensation of* 8-3′-*Chloropropylamino*-6-*methoxyquinoline and Piperazines.*—8-[3-(4-3′-*Hydroxybutylpiperazin*-1-*yl*)*propylamino*]-6-*methoxyquinoline*. 8-3′-Chloropropylamino-6-methoxyquinoline hydrochloride (2·9 g.) and 1-3′-hydroxybutylpiperazine (4·75 g., 3 equiv.) were heated at 130° for 6 hr. The dark red melt was dissolved in 2N-hydrochloric acid, and the solution was made alkaline. The base was extracted with ether, a small amount of tar being left undissolved. The ether extract was dried (Na_2SO_4) and evaporated, leaving the *base*, m. p. 101—104°. Recrystallisation from ethyl acetate furnished cream-coloured needles, m. p. 109—109·5° (Found: C, 67·4; H, 8·9; N, 14·9. $C_{21}H_{32}N_4O_2$ requires C, 67·7; H, 8·7; N, 15·0%).

Method 3a. *Reduction of* 8-ω-*piperazin*-1′-*ylacylaminoquinolines* (IV). The quinoline halogeno-amides (VIII) (Table 2) were prepared by the following method.

8-γ′-*Chlorobutyramido*-6-*methoxyquinoline*. A solution of 8-amino-6-methoxyquinoline (78 g.) in acetone (600 ml.) was stirred with anhydrous sodium carbonate (72 g.) while a solution of γ-chlorobutyryl chloride [26] (67 g.) in acetone (150 ml.) was slowly added. The mixture was heated under reflux for 4 hr. and then filtered hot. Acetone was distilled from the filtrate, leaving a residue which crystallised from aqueous alcohol (10%) as white prisms (104 g.), m. p. 69—71°.

8-ω-*Piperazin*-1′-*ylacylaminoquinolines* (IV) (Table 3) were prepared by condensation of the foregoing halogeno-amides with piperazines, four methods being used.

(A) 8-[3-(4-2′-*Hydroxypropylpiperazin*-1-*yl*)*propionamido*]-6-*methoxyquinoline*. A solution of 8-β-chloropropionamido-6-methoxyquinoline (13·3 g.) and 1-3′-hydroxypropylpiperazine (10·8 g., 1·5 equiv.) in benzene (75 ml.) was heated under reflux for 18 hr. When cold the mixture was extracted with 2N-acetic acid. The extract (charcoal) was made alkaline and the basic amide (14 g.) thus liberated was collected, washed, dried, and recrystallised from benzene–cyclohexane forming almost white leaflets, m. p. 132—133°.

(B) 8-[δ-(4-*Isopropylpiperazin*-1-*yl*)*valeramido*]-6-*methoxyquinoline*. A mixture of 8-δ-bromovaleramido-6-methoxyquinoline (13·5 g.) and 1-isopropylpiperazine (7·7 g., 1·5 equiv.) was kept at 100° for 6 hr. The melt was then dissolved in 2N-acetic acid, and the solution was made alkaline and extracted with benzene, some amorphous material remaining undissolved. The extract was dried (Na_2SO_4) and evaporated, leaving the amide as a gum which was used for reduction. It was characterised as the di(hydrogen maleate), formed by mixing ethyl acetate solutions of the components, and crystallised from ethanol as white leaflets, m. p. 181—182°.

(C) This was essentially method A except that one equivalent only of the piperazine was used and 1·1 equivalents of triethylamine.

(D) 6-*Methoxy*-8-(ω-*piperazin*-1′-*ylacylamino*)*quinolines* (IV; R′ = H). The 6-methoxy-8-(ω-chloro- or -bromo-acylamino)quinoline (VIII; X = Cl or Br) (0·1 mol.) and anhydrous piperazine (34·4 g., 0·4 mol.) in dry benzene (300 ml.) were boiled under reflux for 4—6 hr. and left overnight. The mixture was filtered from piperazine hydrohalide and 1,4-di-[ω-*N*-(6-methoxy-8-quinolyl)carbamoylalkyl]piperazine (IX; Table 4). The diamine (IX) was separated from the piperazine hydrohalide by washing with water. To isolate the amide (IV; $n = 3$, R′ = H) the benzene filtrate was extracted with water (3 × 100 ml.). When the aqueous extracts cooled, the amide (IV; $n = 3$, R′ = H) separated as colourless needles of the hydrate. The latter lost water on exposure, or by azeotropic distillation with benzene, to give the anhydrous compound, which was initially oily but later solidified and was recrystallised from light petroleum (b. p. 60—80°). The anhydrous amide is readily soluble in cold water, but separates as an oil on warming. On storage the aqueous solution deposits the crystalline hydrate. To isolate the amides (IV; $n = 2$, 4, 5, and 6; R′ = H) the benzene filtrate was evaporated to dryness and the residue dissolved in water. The solution was filtered from further diamide (IX) and extracted several times with chloroform. The residue left after removal of the chloroform was recrystallised to give the pure amide.

[26] Reppe, *Annalen*, 1955, **596**, 190.

The amides were reduced to 6-alkoxy-8-(ω-piperazin-1′-ylalkylamino)quinolines (Table 1) by essentially the following method. In some examples the yield of trihydrochloride was substantially below that expected from the distilled base used in its preparation. We attribute this disparity at least partly to the presence of tetrahydroquinolines in the distillate. The boiling ranges given in the Table are only approximate.

A solution of 6-methoxy-8-[5-(4-methylpiperazin-1-yl)pentanoylamino]quinoline (Table 3) (27·5 g.) in ether (412 ml.) was added to a stirred solution of lithium aluminium hydride (5·4 g., 2 mol.) in ether (108 ml.). The mixture was stirred under reflux for 2 hr., then cooled in ice and treated successively with water (5·4 ml.), 15% aqueous sodium hydroxide (5·4 ml.), and water (16·2 ml.) to decompose the complexes. Filtration was rapidly effected and the ethereal solution was dried, evaporated, and distilled. The product (22·4 g.) was collected at *ca.* 210—214°/0·01 mm. and was converted into the trihydrochloride which crystallised from methanol in deep yellow needles (22 g.), rapidly hydrated on exposure and then having m. p. 236—238°.

Some of the bases crystallised before and some after distillation and the following were obtained pure. 8-[3-(4-2′-*Hydroxyethylpiperazin*-1-*yl*)*propylamino*]-6-*propoxyquinoline* crystallised from cyclohexane in white needles, m. p. 97·5° (Found: C, 67·6; H, 9·3; N, 14·9. $C_{21}H_{32}N_4O_2$ requires C, 67·7; H, 8·7; N, 15·0%).

6-*Ethoxy*-8-[5-(4-*methylpiperazin*-1-*yl*)*pentylamino*]*quinoline* crystallised from light petroleum (b. p. 60—80°) in pale yellow prisms, m. p. 58·5—60° (Found: C, 70·5; H, 9·0; N, 15·4. $C_{21}H_{32}N_4O$ requires C, 70·7; H, 9·0; N, 15·7%).

8-[6-(4-2′-*Hydroxypropylpiperazin*-1-*yl*)*hexylamino*]-6-*methoxyquinoline* crystallised from ethyl acetate in cream-coloured prisms, m. p. 108—109·5° (Found: C, 68·8; H, 9·1; N, 13·7. $C_{23}H_{36}N_4O_2$ requires C, 69·0; H, 9·1; N, 14·0%).

Method 3b. *Reduction of Amides* (IV) *with Ethoxycarbonyl Groups*. Essentially the same method as 3a except that 2·5 mol. of lithium aluminium hydride were used. *N*-Ethoxycarbonyl groups were converted into *N*-methyl, and *N*-ethoxycarbonylmethyl groups into *N*-hydroxyethyl.

Method 4. *Reduction of* 8-(3-*Oxo*-3-*piperazin*-1′-*ylpropylamino*)*quinolines* (V).—(i) 1-β-*Chloropropionyl*-4-*methylpiperazine hydrochloride*. A suspension of anhydrous sodium carbonate (12·7 g.) in 1-methylpiperazine (10 g.) and dry acetone (100 ml.) was mechanically stirred and cooled in ice. β-Chloropropionyl chloride (14 g.) was added dropwise at such a rate that the temperature of the mixture remained between 20° and 25°. Then the mixture was stirred in the ice-bath for a further 3 hr. The solid was filtered off and washed with dry acetone, and to the filtrate was added an excess of ethereal hydrogen chloride. More dry ether was added to complete the precipitation of the cream-coloured solid, which was collected, washed with ether, and dried in a vacuum-desiccator (19·3 g.). The *hydrochloride* crystallised from alcohol in colourless plates, m. p. 189° (effervescence) (Found: C, 42·6; H, 6·7; N, 12·4. $C_8H_{16}Cl_2N_2O$ requires C, 42·3; H, 7·1; N, 12·4%).

(ii) 1-β-*Chloropropionyl*-4-*ethoxycarbonylpiperazine*. 1-Ethoxycarbonylpiperazine (15·8 g.) was treated with β-chloropropionyl chloride (12·7 g.) in the presence of anhydrous sodium carbonate (10·6 g.) under conditions similar to those described above. The filtered acetone solution was evaporated to dryness and the residue was distilled to give a pale yellow oil boiling at 164—166°/0·5 mm., with some decomposition. Analyses for this material were somewhat high in carbon and low in chlorine.

(iii) 8-[3-(4-*Methylpiperazin*-1-*yl*)-3-*oxopropylamino*]-6-*methoxyquinoline*. A solution of 8-amino-6-methoxyquinoline (8·7 g.) and 1-β-chloropropionyl-4-methylpiperazine hydrochloride (11·35 g.) in propan-1-ol (50 ml.) was refluxed for 93 hr. The orange solid which had separated towards the end of this time was filtered from the cooled solution. It was 8-[3-(4-*methylpiperazin*-1-*yl*)-3-*oxopropylamino*]-6-*methoxyquinoline dihydrochloride* (10·0 g.), crystallising from aqueous ethanol in yellow needles, m. p. 232° (effervescence) (Found: Cl, 16·9; N, 13·5; loss at 110°/vac., 4·0. $C_{18}H_{26}Cl_2N_4O_2,H_2O$ requires Cl, 16·9; N, 13·4; H_2O, 4·3%).

The base crystallised from aqueous methanol as needles of the *dihydrate*, m. p. unsharp 68—78° (Found: C, 59·7; H, 7·7; N, 15·4. $C_{18}H_{24}N_4O_2,2H_2O$ requires C, 59·3; H, 7·7; N, 15·4%).

(iv) 8-[3-(4-*Ethoxycarbonylpiperazin*-1-*yl*)-3-*oxopropylamino*]-6-*methoxyquinoline*. A mixture of the 8-aminoquinoline (17·4 g.) and 1-β-chloropropionyl-4-ethoxycarbonylpiperazine (12·4 g.) was heated at 130° (bath-temperature) for 6 hr. The mass was extracted with chloroform

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(*ca.* 100 ml.) and the insoluble hydrochloride of the starting quinoline was filtered off. The chloroform solution was evaporated to dryness and the residual viscous oil was boiled with ether and then cooled. The pale yellow solid (13·9 g.) was collected and recrystallised from aqueous methanol, to give pale yellow prisms, m. p. 133—134°, of 8-[3-(4-*ethoxycarbonylpiperazin*-1-*yl*)-3-*oxopropylamino*]-6-*methoxyquinoline* (Found: C, 62·3; H, 6·7; N, 14·5. $C_{20}H_{26}N_4O_4$ requires C, 62·2; H, 6·8; N, 14·5%). The *hydrochloride* crystallised from methanol–ethyl acetate in yellow needles, m. p. 192—194° (effervescence) (Found: Cl, 8·6; N, 13·3. $C_{20}H_{27}ClN_4O_4$ requires Cl, 8·4; N, 13·3%).

The foregoing amides, when reduced with lithium aluminium hydride in ether by the general method described above, both gave, in yields of 30% and 38% respectively, pure 6-*methoxy*-8-[3-(4-*methylpiperazin*-1-*yl*)*propylamino*]*quinoline trihydrochloride*, identical with the material described in Table 1.

Method 5. *Reduction of the Quinoline Diamides* (VI).—1-β-*Carboxypropionyl*-4-*methylpiperazine*. Succinic anhydride (10 g.) was added cautiously to a solution of 1-methylpiperazine (10 g.) in chloroform (25 ml.). The mixture was heated on the steam-bath for 1 hr., and then evaporated to dryness. The residue crystallised from slightly aqueous acetone to give 1-β-*carboxypropionyl*-4-*methylpiperazine* as prisms, m. p. 95—96° (Found: C, 49·7; H, 8·1; N, 12·6; loss at 80°/vac., 8·3. $C_9H_{16}N_2O_3,H_2O$ requires C, 49·5; H, 8·3; N, 12·8; H_2O, 8·3%). The *hydrochloride*, prepared in alcohol, crystallised from alcohol in prisms, m. p. 177—178° (Found: C, 45·6; H, 7·3; Cl, 15·2; N, 11·9. $C_9H_{17}ClN_2O_3$ requires C, 45·7; H, 7·2; Cl, 15·0; N, 11·8%).

6-*Methoxy*-8-[4-(4-*methylpiperazin*-1-*yl*)-1,4-*dioxobutylamino*]*quinoline*. (*a*) To a mixture of 8-amino-6-methoxyquinoline (1 g.) and the preceding piperazine derivative (1·3 g.) in methylene dichloride (20 ml.) was added *NN'*-dicyclohexylcarbodi-imide (1·2 g.), and the whole was left at room temperature for 17 hr. The solid was collected and shown to be *NN'*-dicyclohexylurea (m. p. 232—233°). The filtrate was evaporated to dryness, and the residue was shaken with dilute hydrochloric acid (5 ml. of 2N-acid + 25 ml. of water). The filtered solution was basified, and the resulting suspension was shaken with ether. The white solid was collected and recrystallised from ethyl acetate, to give the *diamide* (see Table 5) (800 mg.). It formed a *hydrochloride*, crystallising from alcohol as colourless needles, m. p. 227—228° (Found: Cl, 9·0; N, 14·4. $C_{19}H_{25}ClN_4O_3$ requires Cl, 9·0; N, 14·3%).

(*b*) To a solution of *N*-(6-methoxy-8-quinolyl)succinamic acid [21] (2·74 g.) and 1-methylpiperazine (1 g.) in dioxan (25 ml.), was added *NN'*-dicyclohexylcarbodi-imide (2·04 g.). After 20 hr. the insoluble *NN'*-dicyclohexylurea (1·25 g.) was collected, and the filtrate was evaporated to dryness. The residue was shaken with N-acetic acid (50 ml.) and chloroform (25 ml.), and the aqueous solution was separated and made alkaline. The precipitated solid (1·05 g.) was shown to be identical (m. p. and mixed m. p.) with the diamide described above.

The preparations of all the diamides in Table 5 were carried out by the general method exemplified by the following:

8-[4-(4-*Ethoxycarbonylmethylpiperazin*-1-*yl*)-1,4-*dioxobutylamino*]-6-*methoxyquinoline*. A solution of succinic anhydride (40 g.) and 1-ethoxycarbonylmethylpiperazine (68·8 g.) in chloroform (400 ml.) was refluxed for 1 hr. 8-Amino-6-methoxyquinoline (69·6 g.) was added, and the solution was cooled. *NN'*-Dicyclohexylcarbodi-imide (90·6 g.) was added gradually with shaking and cooling, and then the mixture was left overnight. The *NN'*-dicyclohexylurea (82 g.) was filtered off and washed with chloroform, and the filtrate was evaporated to dryness. The residue was warmed with N-hydrochloric acid (500 ml.), the solution was filtered, and the filtrate was made alkaline with cooling and stirring. Ether (400 ml.) was added and the mixture was stirred vigorously for 1 hr., during which the suspended oil was replaced by a white solid. This required *diamide* (140 g.) (Table 5) was collected and washed with water and ether.

The reductions of the diamides were carried out by methods similar to the general method described above for the monoamides, tetrahydrofuran being used as solvent. For diamides with no other reducible groups, 3 mol. of lithium aluminium hydride were used, and for diamides having also a CO_2Et group, 4 mol.

Attempted reaction of N-(6-*methoxy*-8-*quinolyl*)*succinamic acid with* 1-2′-*hydroxyethylpiperazine*. To a solution of the succinamic acid (2·5 g.) and 1′-2-hydroxyethylpiperazine (1·2 g.) in chloroform (50 ml.) was added *NN'*-dicyclohexylcarbodi-imide (2 g.). After 48 hr., the solution had deposited only a little solid which was removed by filtration. The filtrate was evaporated to dryness, and the residue was extracted with warm N-acetic acid, from which

only a trace of material was deposited on basification. The acid-insoluble material (2·9 g.) crystallised from methanol as fine needles, m. p. 130—132°, of NN′-*dicyclohexyl*-N-[4-(6-*methoxy*-8-*quinolylamino*)-1,4-*dioxobutyl*]*urea* (XIII) (Found: C, 67·7; H, 7·7; N, 11·7. $C_{27}H_{38}N_4O_4$ requires C, 67·5; H, 7·6; N, 11·7%).

1,2,3,4-*Tetrahydro*-6-*methoxy*-8-(5-*piperazin*-1′-*ylpentylamino*)*quinoline*. 6-Methoxy-8-(5-piperazin-1′-ylpentanoylamino)quinoline (IV; $n = 4$, R′ = H) (17 g.) in tetrahydrofuran (160 ml.) was reduced with lithium aluminium hydride (6 g.) in ether (200 ml.). The crude base was distilled (b. p. 244—250°/0·1 mm.) and converted into the trihydrochloride, which, crystallised from ethanol containing a few drops of water, gave orange 6-methoxy-8-(5-piperazin-1′-ylpentylamino)quinoline trihydrochloride (II; $n = 5$, R = 6-MeO, R′ = H) (7 g.), m. p. 265° (decomp.). The filtrate, on dilution with ether, gave a yellow solid which was freed from tar by washing it with a little hot ethanol and recrystallised from ethanol containing a very little water, to give 1,2,3,4-*tetrahydro*-6-*methoxy*-8-(5-*piperazin*-1′-*ylpentylamino*)*quinoline trihydrochloride* (4 g.), yellow prisms, m. p. 235° (decomp.) (Found: C, 50·5; H, 7·9; N, 12·4. $C_{19}H_{35}Cl_3N_4O,\frac{1}{2}H_2O$ requires C, 50·6; H, 8·0; N, 12·4%).

8-[3-(4-*Ethylpiperazin*-1-*yl*)*propylamino*-1,2,3,4-*tetrahydro*-6-*methoxyquinoline*. A mixture of 6-methoxy-8-(β-piperazin-1-ylpropionamido)quinoline (10 g.), acetic anhydride (20 ml.), and dry benzene (50 ml.) was heated under reflux for ½ hr. After removal of solvent *in vacuo*, the residual gum was dissolved in water and cautiously basified with sodium hydroxide, and the precipitated solid was filtered off, washed with water, and dried. It was recrystallised from benzene to give 8-[β-(4-*acetylpiperazin*-1-*yl*)*propionamido*]-6-*methoxyquinoline* (9·0 g.) as colourless crystals, m. p. 136° (Found: C, 64·3; H, 7·1; Ac, 12·2. $C_{19}H_{24}N_4O_3$ requires C, 64·0; H, 6·8; Ac, 12·1%). The acetyl compound was reduced with lithium aluminium hydride and the crude base was converted into its trihydrochloride. The latter crystallised from aqueous ethanol, to give 8-[3-(4-ethylpiperazin-1-yl)propylamino]-6-methoxyquinoline trihydrochloride (6·2 g.) as deep yellow needles, m. p. 239° (decomp.) unchanged on crystallisation from methanol, or on admixture with the product obtained by method 1.

The filtrate from the first crystallisation gradually deposited light coloured solid (4·0 g.), m. p. 235—236° (decomp.), which after crystallisation from ethanol gave 8-[3-(4-*ethylpiperazin*-1-*yl*)*propylamino*]-1,2,3,4-*tetrahydro*-6-*methoxyquinoline trihydrochloride* as fawn needles (3·2 g.), m. p. 240° (decomp.), depressed on admixture with the foregoing material to 224—228° (decomp.) (Found: C, 49·8; H, 8·3; N, 11·9; Cl, 23·1; loss, 4·5. $C_{19}H_{35}ClN_4O,H_2O$ requires C, 49·6; H, 8·1; N, 12·2; Cl, 23·1; H_2O, 3·9%).

The same compound was obtained by reduction of the corresponding quinoline with an excess of sodium and pentyl alcohol by the method of Barber and Wragg.[27]

6-*Methoxy*-8-(3-*piperazin*-1′-*ylpropylamino*)*quinoline Trihydrochloride* (II; $n = 3$, R = 6-OMe, R′ = H): *Alternative Preparation*.—A solution of potassium hydroxide (6 g.) in water (6 ml.) was added to a solution of 8-[3-(4-ethoxycarbonylpiperazin-1-yl)propylamino]-6-methoxyquinoline (2·8 g.; Table 1) in methanol (56 ml.), and the mixture was heated under reflux for 16 hr. The solution was decanted from inorganic salt and evaporated to small bulk. Water was added and the basic product was isolated with ether and converted into the trihydrochloride (Table 1).

8-[2-(4-*Ethoxycarbonylpiperazin*-1-*ylethyl*)*amino*]-6-*methoxyquinoline Dihydrochloride* (II; $n = 2$, R = 6-OMe, R′ = CO_2Et).—6-Methoxy-8-(2-piperazin-1′-ylethylamino)quinoline (5 g.; Table 1) was dissolved in ethyl acetate and stirred with 0·5N-sodium hydroxide (38·5 ml.) with ice-cooling. Ethyl chloroformate (2·1 g.) in ethyl acetate (10 ml.) was added. After 2 hr. an excess of alkali was added and the ethyl acetate layer was separated and dried (Na_2SO_4). The residue left after evaporation of solvent was converted into the *dihydrochloride* which crystallised from ethanol. The salt (4·6 g.) separated at first as deep yellow prisms, but rapid cooling gave leaflets only, m. p. 199—200° (effervescence) (Found after drying: C, 53·1; H, 6·6; Cl, 16·1; N, 12·9. $C_{19}H_{28}Cl_2N_4O_3$ requires C, 52·9; H, 6·6; Cl, 16·4; N, 13·0%).

8-[4-(4-2′-*Hydroxyethylpiperazin*-1-*yl*)*butylamino*]-6-*methoxyquinoline* (II; $n = 4$, R = 6-OMe, R′ = $CH_2{\cdot}CH_2{\cdot}OH$): *Alternative Preparation*.—A solution of 6-methoxy-8-(4-piperazin-1′-ylbutylamino)quinoline (2·5 g.; Table 1) in methanol (25 ml.) was cooled in ice and treated with ethylene oxide (0·52 g.). The solution was left for several days and then evaporated and distilled. The distillate was converted into the trihydrochloride (Table 1).

[27] Barber and Wragg, *J.*, 1946, 613.

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8-{3-[4-(2,3-Dihydroxypropyl)piperazin-1-yl]propylamino}-6-methoxyquinoline Trihydrochloride [II; $n = 3$, R = 6-OMe, R′ = $CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}OH$].—6-Methoxy-8-(3-piperazin-1′-ylpropylamino)quinoline (3 g.; Table 1) in ethanol (30 ml.) was treated with DL-glycidol (0·8 g.) and left for 4 days. Evaporation of ethanol left a base that was insoluble in ether. It was purified by conversion into the *trihydrochloride* and crystallised first from aqueous ethanol and then from a large volume of methanol, forming yellow prisms (2·3 g.), m. p. 228—230° (decomp.) (Found: C, 47·0; H, 7·1; Cl, 20·4; N, 10·7. $C_{20}H_{32}Cl_2N_4O_3,2H_2O$ requires C, 46·2; H, 7·2; Cl, 20·5; N, 10·8%).

NN′-Di-[4-(6-methoxy-8-quinolylamino)butyl]piperazine (IX; $n = 3$, R = 6-OMe, CH_2 for CO).—The diamide (IX; $n = 3$) (11·3 g.) in tetrahydrofuran (150 ml.) was reduced with lithium aluminium hydride (3 g.) in tetrahydrofuran (150 ml.). The crude product solidified. Several crystallisations from light petroleum (b. p. 60—80°) gave the *compound* (3·4 g.) as pale yellow prisms, m. p. 110—111° (Found: C, 71·0; H, 8·0; N, 15·1. $C_{32}H_{42}N_6O_2$ requires C, 70·9; H, 7·8; N, 15·5%).

The authors thank Mr. P. R. W. Baker for the microanalyses, Dr. A. J. Everett for the ultraviolet absorption spectra and for helpful discussions, and Messrs. D. E. Bays, W. E. Clifford-King, and D. H. Morgan for valuable technical assistance.

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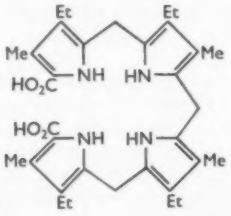
468. *The Formation of Porphyrins by the Cyclisation of Bilenes.*

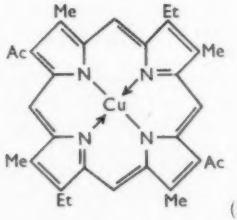
By A. W. JOHNSON and I. T. KAY.

An oxidative cyclisation involving the terminal methyl groups of bilenes and biladienes can be brought about by the action of cupric acetate and yields porphyrins. Reaction of bilene-b derivatives with aluminium chloride causes fission at the terminal methylene bridges and also yields porphyrins by combination of two dipyrromethene fragments.

UNTIL recently there were few methods, which involved the cyclisation of a suitable tetrapyrrolic system, available for the synthesis of porphyrins. Such methods, which offer the possibility of preparing porphyrins with an unsymmetrical arrangement of β-substituents, frequently involved decarboxylations, *e.g.* the cyclisation of the acid (I) with hot formic acid to ætioporphyrin (claimed [1] to be the II isomer).



(I)



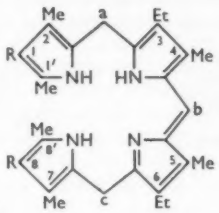
(II)

We have used the oxidation of terminal methyl groups with cupric acetate in methanol to effect cyclisations of linear tetrapyrrolic compounds, and a recent paper [2] describing the use of this reagent at higher temperatures prompts us to record our findings. The American workers [2] studied the oxidative self-condensation of certain 3-(and 4-)acetyl-5-methyldipyrromethanes with cupric acetate in molten naphthalene at 190° and showed

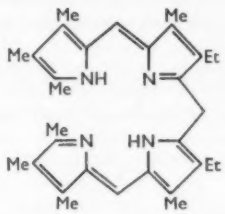
[1] Corwin and Coolidge, *J. Amer. Chem. Soc.*, 1952, **74**, 5196.
[2] Kleinspehn and Corwin, *J. Amer. Chem. Soc.*, 1960, **82**, 2750.

that the main product was the copper complex of diacetyldeuteroætioporphyrin (as II) although other porphyrins were undoubtedly present in the mixture.

The intermediate tetrapyrrolic compounds which we have employed have been of two types. The 1′,8′-dideoxy-1′,8′-dimethylbilene-b (III) derivatives were obtained, following Fischer and Kürzinger,[3] by the condensation of 4,4′-diethyl-5,5′-bismethoxymethyl-3,3′-



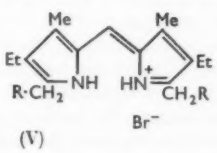
(III)



(IV)

dimethyldipyrromethene with two equivalents of a 2,3,4-trialkylpyrrole. The 1′,8′-dideoxy-1′,8′-dimethylbiladiene-ac (IV) derivatives,* which have not been previously described, were prepared by the reaction of two equivalents of 2-formyl-3,4,5-trimethylpyrrole with either 3,3′-diethyl-4,4′-dimethyldipyrromethane or the corresponding 5,5′-dicarboxylic acid.

The ability of cupric acetate to bring about this type of oxidative cyclisation was revealed by the conversion of 4,4′-diethyl-3,3′,5,5′-tetramethyldipyrromethene hydrobromide [5] (V; R = H) to the cupric derivative of ætioporphyrin II. In another sequence, the benzyl groups of 5,5′-dibenzyloxy-4,4′-diethyl-3,3′-dimethyldipyrromethene (V; R = O·CH_2Ph) were removed by hydrogenolysis, and the resulting dihydroxymethyl derivative (V; R = OH) was treated with cupric acetate to give the copper derivative of ætioporphyrin II (VI) in 21% overall yield.



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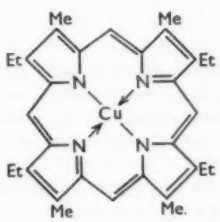

(VI)

The tetrapyrrolic compounds (III; R = Me,Et) and (IV) were cyclised to a porphyrin by treatment with cupric acetate in methanol but when similar reactions were carried out with zinc or cobaltous acetate the products were complexes of type (VII) containing eight pyrrole rings to each metal atom. However, the action of aluminium chloride in pyridine on the bilene-b derivatives also yielded porphyrins and it was of interest to establish whether this cyclisation was operating by a mechanism similar to that brought about by cupric acetate. It was found from the results of *X*-ray powder photographs that the product of cyclisation with aluminium chloride of 1′,8′-dideoxy-1,3,6,8-tetraethyl-1′,2,4,5,7,8′-hexamethylbilene-b (III; R = Et) was ætioporphyrin II

* The nomenclature used in this series is based on that of the bile pigments proposed by Lemberg and Legge,[4] by removal of the two hydroxyl groups at positions 1′ and 8′ by use of the prefix deoxy. The numbering is that shown in Formula (III).

[3] Fischer and Kürzinger, *Z. physiol. Chem.*, 1931, **196**, 213.

[4] Lemberg and Legge, "Hematin Compounds and Bile Pigments," Interscience, New York and London, 1949, p. 105.

[5] Johnson, Kay, Markham, Price, and Shaw, *J.*, 1959, 3416.

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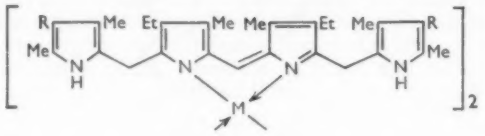
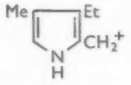
and was identical with that obtained from a similar cyclisation of 1′,8′-dideoxy-3,6-diethyl-1,1′,2,4,5,7,8,8′-octamethylbilene-b (III; R = Me). A different product, a diethylhexamethylporphyrin was obtained from the latter bilene-b by cyclisation with cupric acetate, and the processes are therefore fundamentally different. It is concluded that cupric acetate causes cyclisation of the bilene-b by oxidation of the terminal methyl groups and subsequent cyclisation but that aluminium chloride causes fission of the bilene-b at the methylene groups with a subsequent union of two dipyrromethene fragments.



(VII) R = Me ; M = Zn R = Et ; M = Co^{II}



(VIII)

The unique properties of cupric salts were further revealed by an examination of the acid cyclisation of the various metallic complexes of 4,4′-diethyl-5,5′-bismethoxymethyl-3,3′-dimethyldipyrromethene.[3] No porphyrin was obtained from the cobaltous or zinc complexes (or the free hydrobromide), only a trace (<1%) from the nickel complex, but 10% from the cupric complex. It is assumed that the cobalt, zinc, and nickel complexes, which are normally tetrahedral, must distort appreciably before cyclisation to the planar porphyrin can occur but the cupric complex, which is unstable in the tetrahedral form, is readily transformed to the planar state.

Reduction of the bilene-b derivatives gave the unstable bilanes which could not be isolated pure; treatment of solutions of the bilanes with acids gave porphyrins, presumably by fission of the methylene bridges to the carbonium ions (VIII) which are known to polymerise to porphyrins.[6]

Experimental

Ultraviolet and visible spectra were determined for chloroform solutions, except where otherwise stated. Light petroleum refers to the fraction, b. p. 60—80°.

4,4′-Diethyl-5,5′-bismethoxymethyl-3,3′-dimethyldipyrromethene Hydrobromide.—Prepared by heating the corresponding 5,5′-dibromomethyldipyrromethene under reflux with methanol, this had m. p. 177° [lit.[3] 178°].

Metal Complexes.—(i) The methene hydrobromide (1 g.) in methanol (10 c.c.) was treated with a saturated solution of cupric acetate in ammonia (2·5 c.c.; *d* 0·88), and the solution boiled for 5 min. After cooling, the copper complex was separated, washed with water and methanol, and crystallised from chloroform–methanol (to which several drops of concentrated ammonia solution had been added). It then formed green plates (730 mg.), m. p. 169° (lit.[3] 168°) (Found: N, 8·15. Calc. for $C_{33}H_{54}CuN_4O_4$: N, 8·0%); $\lambda_{max.}$ 475 and 516 mμ (log ε 4·81 and 4·85, respectively).

(ii) Prepared in an analogous manner, by using ammoniacal nickel chloride, the *nickel complex* formed green prisms, m. p. 143° (Found: C, 66·2; H, 8·05; N, 8·2. $C_{33}H_{54}N_4NiO_4$ requires C, 66·2; H, 7·95; N, 8·1%); $\lambda_{max.}$ 235, 392, and 509 mμ (log ε 4·38, 4·13, and 5·03, respectively).

(iii) Prepared similarly by using ammoniacal cobaltous acetate, the *cobalt complex* formed green prisms, m. p. 150° (Found: C, 66·4; H, 8·15; N, 8·5. $C_{33}H_{54}CoN_4O_4$ requires C, 66·15; H, 7·9; N, 8·1%); $\lambda_{max.}$ 234, 379, and 510 mμ (log ε 4·39, 4·22, and 4·07, respectively).

(iv) Prepared similarly by using ethanolic zinc acetate, the *zinc complex* formed yellow plates with a green lustre, m. p. 151° (Found: C, 65·8; H, 7·75; N, 7·9. $C_{33}H_{54}N_4O_4Zn$ requires C, 65·55; H, 7·85; N, 8·05%); $\lambda_{max.}$ 289, 311, and 508 mμ (log ε 3·58, 3·38, and 5·32, respectively).

1′,8′-Dideoxy-3,6-diethyl-1,1′,2,4,5,7,8,8′-octamethylbilene-b Hydrobromide.—4,4′-Diethyl-5,5′-bismethoxymethyl-3,3′-dimethyldipyrromethene hydrobromide (3 g.) in benzene (30 c.c.) and

[6] Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.

2,3,4-trimethylpyrrole (1·9 g.; 2 mols.) were heated under reflux for 30 min. Hot light petroleum (10 c.c.) was then added and the solution was cooled. The *salt* was washed with light petroleum; it crystallised from chloroform–light petroleum as orange plates with a metallic sheen, m. p. 187° (decomp.) (3·5 g.; 84%) (Found: C, 67·3; H, 7·8; N, 9·95. $C_{31}H_{43}BrN_4$ requires C, 67·5; H, 7·85; N, 10·15%); $\lambda_{max.}$ 235, 368, 512 mμ (log ε 4·29, 3·83, and 4·53, respectively).

The *zinc complex* (290 mg.) from this hydrobromide (500 mg.) formed green plates, decomp. >200° (Found: C, 73·8; H, 8·15; N, 11·0. $C_{62}H_{82}N_8Zn$ requires C, 74·15; H, 8·25; N, 11·15%); $\lambda_{max.}$ 233, 356, 373, 513 mμ (log ε 4·53, 4·15, 4·13, and 4·94, respectively).

1′,8′-*Dideoxy*-1,3,6,8-*tetraethyl*-1′,2,4,5,7,8′-*hexamethylbilene-b Hydrobromide.*—Prepared (37%) in an analogous manner from the condensation of cryptopyrrole (2 mol.) with 4,4′-diethyl-5,5′-bismethoxymethyl-3,3′-dimethyldipyrromethene hydrobromide (1 mol.) in benzene, this *salt* formed red-brown hexagonal plates, m. p. 180° (from chloroform–light petroleum) (Found: C, 68·1; H, 7·85; N, 9·55. $C_{33}H_{47}BrN_4$ requires C, 68·35; H, 8·15; N, 9·65%); $\lambda_{max.}$ 235, 368, 512 mμ (log ε 4·26, 3·82, and 4·48, respectively).

The *cobalt complex* (380 mg.) from this hydrobromide (500 mg.) formed green plates, m. p. 230—231° (Found: C, 75·3; H, 8·55; N, 10·45. $C_{66}H_{90}CoN_8$ requires C, 75·2; H, 8·6; N, 10·65%); $\lambda_{max.}$ 233, 382, 521 mμ (log ε, 4·57, 4·29, and 5·07, respectively).

1′,8′-*Dideoxy*-4,5-*diethyl*-1,1′,2,3,6,7,8,8′-*octamethylbiladiene-ac Dihydrochloride.*—Dibenzyl 3,3′-diethyl-4,4′-dimethyldipyrromethane-5,5′-dicarboxylate (5 g.) in methanol (75 c.c.) was hydrogenated at 100°/100 atmos. for 2 hr., Raney nickel being used. After separation of the catalyst, the solution was concentrated to *ca.* 40 c.c. and then cooled. Concentrated hydrochloric acid (3 c.c.) and 3,4,5-trimethylpyrrole-2-aldehyde (2·7 g.; 2 mol.) were then added and the solution kept at room temperature for 2 hr. Water (500 c.c.) was added to the solution which was then extracted with chloroform (*ca.* 250 c.c.), and the chloroform layer dried ($MgSO_4$). After removal of the solvent, the residual *salt* formed red needles with a green lustre (2·2 g.; 41%), m. p. >350°, from chloroform–light petroleum (Found: C, 68·4; H, 7·6; N, 10·2. $C_{31}H_{42}Cl_2N_4$ requires C, 68·75; H, 7·8; N, 10·35%); $\lambda_{max.}$ 291, 371, 457, 527 mμ (log ε 4·41, 4·19, 4·36, and 5·31, respectively).

1′,8′-*Dideoxy*-1,1′,2,3,4,5,6,7,8,8′-*decamethylbiladiene-ac Dihydrochloride.*—3,3′4,4′-Tetramethyldipyrromethane-5,5′-dicarboxylic acid (1·1 g.) was suspended in methanol (15 c.c.) containing concentrated hydrochloric acid (5 c.c.). 3,4,5-Trimethylpyrrole-2-aldehyde (1 g.; 2 mol.) was then added, and the solution was heated (steam-bath) for 20 min. On cooling, the *product* which separated was washed with a little methanol; it crystallised from chloroform–light petroleum as brown rods with a green lustre (1·4 g.; 72%), m. p. >350° (Found: C, 67·4; H, 6·9; N, 10·7. $C_{29}H_{38}Cl_2N_4$ requires C, 67·8; H, 7·45; N, 10·9%), $\lambda_{max.}$ 290, 370, 456, and 526 mμ (log ε 3·35, 4·12, 4·32, and 5·23, respectively).

5,8-*Diethyl*-1,2,3,4,6,7-*hexamethylporphyrin.*—1′,8′-Dideoxy-3,6-diethyl-1,1′,2,4,5,7,8,8′-octamethylbilene-b hydrobromide (500 mg.) and cupric acetate (1 g.) in methanol (100 c.c.) were heated under reflux for 48 hr. The solvent was then removed by distillation, the residue dissolved in chloroform (*ca.* 40 c.c.), and this solution set aside over anhydrous potassium carbonate for 2 hr. The solid was separated, and the filtrate concentrated to *ca.* 20 c.c. and chromatographed on alumina (Spence type H). The elution of the metal porphyrin was followed by means of a hand spectroscope. After removal of the solvent from the porphyrin fraction, the residue crystallised from chloroform–methanol as blue needles (140 mg.; 30%), m. p. >350° [Found: C, 70·1; H, 6·05; N, 10·8; residue (CuO), 15·5. $C_{30}H_{32}CuN_4$ requires C, 70·35; H, 6·3; N, 10·95; CuO, 15·5%]; $\lambda_{max.}$ 237, 328, 397, 525, and 562 mμ (log ε 4·45, 4·24, 5·56, 4·11, and 4·40, respectively). The *porphyrin–copper complex* (100 mg.), suspended in concentrated sulphuric acid (6 c.c.), was heated (steam-bath) for 5 min. The solution was cooled, diluted with water, basified (NH_4·OH), and extracted with chloroform, and the dried ($MgSO_4$) chloroform layer chromatographed on alumina. The porphyrin fraction yielded steel-blue prismatic needles (65 mg.) from chloroform–methanol (Found: C, 79·8; H, 7·45; N, 12·1. Calc. for $C_{30}H_{34}N_4$: C, 79·95; H, 7·6; N, 12·45%); $\lambda_{max.}$ 269, 398, 497, 532, 566, and 620 mμ (log ε 3·91, 5·21, 4·13, 3·99, 3·82, and 3·67 respectively).

Ætioporphyrin IV Copper Complex.—1′,8′-Dideoxy-1,3,6,8-tetraethyl-1′,2,4,5,7,8′-hexamethylbilene-b hydrobromide (1 g.) in methanol (160 c.c.) was treated with cupric acetate (2 g.), and the solution heated under reflux for 48 hr. The metal porphyrin after chromatography and isolation in the usual manner formed red felted needles (204 mg.; 22%), m. p. 292—293°, from

chloroform–methanol [Found: C, 70·8; H, 6·75; N, 10·2; Ash (CuO), 14·8. Calc. for $C_{32}H_{36}CuN_4$: C, 71·15; H, 6·7; N, 10·35; CuO, 14·7%]; $\lambda_{max.}$ 238, 327, 397, 524, and 561 mμ (log ε 4·45, 4·24, 5·56, 4·10, and 4·38, respectively).

1,2-Diethyl-3,4,5,6,7,8-hexamethylporphyrin Copper Complex.—1′,8′-Dideoxy-4,5-diethyl-1,1′,2,3,6,7,8,8′-octamethylbiladiene-ac dihydrochloride (500 mg.) in methanol (100 c.c.) was treated with cupric acetate (1 g.), and the solution heated under reflux for 48 hr. The *metal porphyrin* was isolated by chromatography in the usual manner and formed blue needles (82 mg.; 17%) from chloroform–methanol [Found: C, 70·2; H, 6·3; N, 11·1; Ash (CuO), 15·5. $C_{30}H_{32}CuN_4$ requires C, 70·35; H, 6·3; N, 10·95; CuO, 15·1%]. Its light absorption was identical with that of the copper complex of 5,8-diethyl-1,2,3,4,6,7-hexamethylporphyrin (above).

Ætioporphyrin.—1′,8′-Dideoxy-1,3,6,8-tetraethyl-1′,2,4,5,7,8′-hexamethylbilene-b hydrobromide (500 mg.) in ethanol (40 c.c.) was reduced over Adams's catalyst. After 2 hr. the solution was colourless, and the catalyst was removed by filtration. Concentrated hydrochloric acid (5 c.c.) was then added and the solution refluxed for 3 hr. Water (200 c.c.) was added, the solution basified with ammonia and extracted with chloroform, and the dried ($MgSO_4$) chloroform layer chromatographed on alumina. The porphyrin fraction yielded purple needles (15 mg.) from chloroform–methanol (Found: N, 11·8. Calc. for $C_{32}H_{38}N_4$: N, 11·7%); $\lambda_{max.}$ 270, 399, 498, 533, and 620 mμ (log ε 3·38, 5·21, 4·09, 3·98, 3·79, and 3·66, respectively).

Ætioporphryin II and Metal Complexes.—(i) 1′,8′-Dideoxy-3,6-diethyl-1,2,4,5,7,8,8′-octamethylbilene-b hydrobromide (1 g.) in dry pyridine (20 c.c.) was treated with anhydrous aluminium chloride (1 g.), and the mixture heated (steam-bath) for 30 min. The resultant dark brown solution was kept overnight at room temperature, poured into water, and thoroughly extracted with chloroform (3 × 100 c.c.); the combined chloroform extracts were dried ($MgSO_4$) and evaporated to dryness, traces of pyridine being removed under reduced pressure. The residue was dissolved in chloroform (20 c.c.) and, after chromatography, the porphyrin fraction yielded purple needles (120 mg.; 27%) from chloroform–methanol (Found: C, 80·4; H, 8·15; N, 11·8. Calc. for $C_{32}H_{38}N_4$: C, 80·3; H, 8·0; N, 11·7%); $\lambda_{max.}$ 269, 398, 497, 533, 566, and 620 mμ (log ε 3·88, 5·2, 4·11, 3·98, 3·81, and 3·66, respectively).

(ii) The previous experiment was repeated with 1′,8′-dideoxy-1,3,6,8-tetraethyl-1′,2,4,5,7,8′-hexamethylbilene-b hydrobromide (1 g.), and the porphyrin isolated in an identical manner (87 mg.; 21%) (Found: C, 80·0; H, 7·9; N, 11·6%). The light absorption was identical with that of the previous preparation.

(iii) 4,4′-Diethyl-3,3′,5,5′-tetramethyldipyrromethene hydrobromide (1 g.) in methanol (160 c.c.) was treated with cupric acetate (3 g.) and the solution heated under reflux for 48 hr. The solvent was then removed by distillation, chloroform (50 c.c.) added to the residue, and the solution dried (anhydrous K_2CO_3). The solution was then concentrated to *ca.* 30 c.c. and, after chromatography, the porphyrin fraction yielded red-brown felted needles (72 mg.; 9%) from chloroform–glacial acetic acid (Found: C, 71·2; H, 6·95; N, 9·95. Calc. for $C_{32}H_{36}CuN_4$: C, 71·15; H, 6·7; N, 10·35%); $\lambda_{max.}$ 328, 398, 525, and 562 mμ (log ε 4·22, 5·57, 4·07, and 4·36, respectively).

(iv) Glacial acetic acid (2·5 c.c.) was added dropwise to refluxing solutions of various metal complexes (500 mg.) of 4,4′-diethyl-5,5′-bismethoxymethyl-3,3′-dimethyldipyrromethene in methanol (100 c.c.) during 10 min. The mixture was heated under reflux for a further 1 hr., then evaporated to dryness, and the residue dissolved in chloroform (20 c.c.) and chromatographed on alumina. The following yields were obtained: Cu^{II} (35 mg.; 10%); Co^{II}, nil; Zn, nil; Ni^{II}, trace (<1%); free hydrobromide, nil. The light absorption of the copper ætioporphyrin II complex was identical with that of the previous preparation.

(v) 5,5′-Bisbenzyloxymethyl-4.4′-diethyl-3,3′-dimethyldipyrromethene hydrobromide (500 mg.; see below), in ethanol (20 c.c.) containing fused sodium acetate (100 mg.), was hydrogenated over Adams's catalyst. Hydrogen (2 mol.) was rapidly absorbed and, after removal of the catalyst, cupric acetate (300 mg.) was added to the solution which was then heated under reflux for 1 hr. The metal porphyrin (52 mg.; 21%) was isolated as in the previous preparations.

5,5′-Bisbenzyloxymethyl-4,4′-diethyl-3,3′-dimethyldipyrromethene Hydrobromide.—The corresponding 5,5′-bisbromomethyldipyrromethene hydrobromide (13 g.) was suspended in benzyl alcohol (80 c.c.) and heated (steam-bath) until it had all dissolved. Ethyl acetate (80 c.c.) was then added to the hot solution, and on cooling, the *benzyloxy-compound* crystallised. It was separated and washed with ethyl acetate; it crystallised from ethyl acetate as golden-orange

needles (9·6 g.; 72%), m. p. 169—170° (decomp.) (Found: C, 68·1; H, 7·1; N, 4·85. $C_{31}H_{37}BrN_2O_2$ requires C, 67·75; H, 6·8; N, 5·0%); $\lambda_{max.}$ 380 and 493 mμ (log ε 3·88 and 5·52, respectively).

We thank the Department of Scientific and Industrial Research for a Maintenance Grant to one of us (I. T. K.).

THE UNIVERSITY, NOTTINGHAM. [*Received, December 2nd,* 1960.]

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469. *Diphosphine Dioxides. Part II.*[1] *Some Diphosphine Dioxides with Mono-, Di-, and Tri-methylene Bridges.*

By GENNADY M. KOSOLAPOFF and ROBERT F. STRUCK.

Various routes for possible synthesis of compounds of type $[R_2P(O)]_2[CH_2]_x$ with $x = 1$—3 were examined and several representative members of the group were prepared.

THE present paper continues the report of our work on synthetic routes to diphosphine dioxides containing polymethylene bridges of varying lengths.[1]

The synthesis of such dioxides with fewer than four methylene groups in the bridge cannot be accomplished by the di-Grignard reagent route used by us previously. Accordingly, we examined a number of other routes, most of which were found to be unworkable or otherwise unattractive.

One of the more fruitful approaches was the reaction of glycol ditoluene-*p*-sulphonates with the Grignard reagents based on secondary phosphine oxides:

$$2R_2P(O)\cdot MgX + (p\text{-}Me\cdot C_6H_4\cdot SO_3)_2[CH_2]_x \longrightarrow R_2P(O)\cdot[CH_2]_x\cdot P(O)R_2 + 2p\text{-}Me\cdot C_6H_4\cdot SO_3\cdot MgX$$

This reaction gave acceptable yields of several dioxides with the ethylene and the trimethylene bridge, but failed for the monomethylene member. A similar reaction employing ethylene bromide in place of the ethylene disulphonate also gave a modest yield of the expected dioxide; this is not surprising in view of the rather high reactivity of ethylene halides.

The second route which was productive, but to a much more limited degree, was that passing through the tetrachlorides of the respective diphosphonic acids:

$$(RO)_2P(O)\cdot[CH_2]_x\cdot P(O)(OR)_2 \longrightarrow Cl_2P(O)\cdot[CH_2]_x\cdot P(O)Cl_2 \longrightarrow R_2P(O)\cdot[CH_2]_x\cdot P(O)R_2$$

This route, which appears superficially attractive, proved much less so in performance. We had explored it rather earnestly before publication [2] of its use for the synthesis of some diphosphine dioxides with a monomethylene bridge; it is this publication that prompted us to report our work at this time.

The conversion of esters of phosphonic acids into phosphonic dichlorides is an old reaction which may be represented simply as follows:

$$R\cdot P(O)(OR)_2 + 2PCl_5 \longrightarrow R\cdot P(O)Cl_2 + 2RCl + 2POCl_3$$

It appeared logical to expect that a similar reaction applied to the esters of diphosphonic acids should lead to formation of the corresponding bisdichlorides $Cl_2P(O)\cdot[CH_2]_x\cdot P(O)Cl_2$. However, the reaction proved to be much more complex than might have been expected; treatment of tetra-alkyl diphosphonates with the theoretically required four-molar quantity of phosphorus pentachloride, under a variety of conditions, yielded products which had a

[1] Part I, *J.*, 1959, 3950.
[2] Burke, Richard, Sakurai, O'Laughlin, and Banks, Amer. Chem. Soc. 138th Meeting, Abs., p. 13B.

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behaviour pattern unexpected of the phosphonic chlorides. The substances were generally insoluble in common organic solvents and usually contained far smaller amounts of chlorine than necessary for the indicated tetrachlorides. Sublimation of such products under a high vacuum did result in volatilization of very small portions of material that had the expected chlorine content, but the bulk of the residual material contained little or no chlorine. It is our opinion, therefore, that the reaction of phosphorus pentachloride with esters of diphosphonic acids is very prone to afford anhydrides, probably of intermolecular type; such reactions are common among organophosphorus compounds:

$$\rangle P(O)Cl + RO{\cdot}P(O)\langle \longrightarrow RCl + \rangle P(O){-}O{-}P(O)\langle$$

However, such reactions do not usually obtrude on the formation of phosphonic dichlorides from esters of monophosphonic acids. Owing to the general intractability of the presumably intermolecular anhydrides, we were unable to secure any further ideas about their probable structures. It is of interest also that specimens of diphosphonic tetrachlorides, specifically the ethylene member, which had been purified by crystallization from phosphorus oxychloride as described by Petrov *et al.*[3] and contained the expected amount of chlorine, nevertheless gave only minute yields of the expected diphosphine dioxides in prolonged reactions with Grignard reagents. This appears to be a further argument against the acceptance of the substances as true diphosphonic tetrachlorides. It is very likely that a large part of the chlorine content of such specimens is located on the bridge between the phosphorus atoms, rather than at the latter. Certainly, recent work by Petrov *et al.*[3] indicates the ready substitution of bridge-hydrogen atoms by chlorine of phosphorus pentachloride, which would lead to such substances. We conclude, therefore, that the reaction

$$(RO)_2P(O){\cdot}[CH_2]_x{\cdot}P(O)(OR)_2 + 4PCl_5 \longrightarrow Cl_2P(O){\cdot}[CH_2]_x{\cdot}P(O)Cl_2 + 4RCl + 4POCl_3$$

takes place only to a minor degree, being overshadowed by the anhydride formation which evidently occurs between further ester and the initially formed partial chlorides.

Synthesis of diphosphine dioxides with $x = 1$ or 2 may be projected through a variety of routes involving an intermediate of the general formula $R_2P(O){\cdot}CH_2Cl$. Thus, coupling of two such units by the action of an active metal should form diphosphine dioxides with $x = 2$, whilst an Arbuzov reaction with a trialkyl phosphite should yield an ester readily convertible into the desired dioxide:

$$R_2P(O){\cdot}CH_2Cl \xrightarrow{M} R_2P(O){\cdot}CH_2{\cdot}CH_2{\cdot}P(O)R_2$$

$$R_2P(O){\cdot}CH_2Cl \xrightarrow{P(OR)_3} R_2P(O){\cdot}CH_2{\cdot}P(O)(OR)_2 \longrightarrow R_2P(O){\cdot}CH_2{\cdot}POCl_2 \longrightarrow R_2P(O){\cdot}CH_2{\cdot}P(O)R_2$$

For a synthesis of the necessary tertiary phosphine oxides with one chloromethyl group, we first turned to the reaction of diazomethane with phosphinyl chlorides:

$$R_2P(O)Cl + CH_2N_2 \longrightarrow R_2P(O){\cdot}CH_2Cl + N_2$$

This reaction had been reported some time ago by Saunders *et al.*[4] in case of a structurally similar dialkyl phosphorofluoridate:

$$(RO)_2P(O)F + CH_2N_2 \longrightarrow (RO)_2P(O){\cdot}CH_2F$$

However, many attempts to carry out this reaction with phosphinyl chlorides, both at low temperatures and at the boiling point of ether (the highest temperature which we felt

[3] Petrov, Maklyaev, and Bliznyuk, *Zhur. obshchei Khim.*, 1960, **30**, 1608.
[4] Saunders, Stacey, Wild, and Wilding, *J.*, 1948, 699.

would be safe for the reagent used) failed to yield any of the expected chloromethyl compound: only unchanged starting material and varying amounts of evidently polymeric solids or semisolids were isolated. Evidently the phosphinyl group prevents the expected reaction of diazomethane with compounds of this group. Accordingly, we attempted to circumvent this problem by treating the tervalent phosphorus compound (phosphorus trichloride) with diazomethane, after which the resulting dichlorochloromethylphosphine was subjected to alkylation with various organometallic reagents (magnesium or lithium); again, none of the desired dialkylchloromethylphosphine oxides was isolated and only semi-solid polymeric materials were formed, along with some tertiary phosphine oxides resulting from alkylation at all three sites of possible reaction.

Having been able to prepare the desired dioxides with $x = 2$ by other routes, we explored further the possibilities of a synthesis of a dialkylchloromethylphosphine oxide as a precursor for the dioxides with $x = 1$. Chlorination of trimethylphosphine oxide under controlled conditions could be expected to yield this substance; however, chlorination under ultraviolet illumination at a variety of temperatures, with or without an activating catalyst (antimony chloride), failed to yield the expected product. Curiously, this treatment was quite effective in a progressive cleavage of the methyl groups from the phosphorus atom and such reactions yielded varying amounts of dimethylphosphinyl chloride, methylphosphonic dichloride, and phosphorus oxychloride. This dealkylation appears to be a novel reaction of trimethylphosphine oxide.

Further, we treated trimethylphosphine oxide with metallic sodium, in the hope of forming a sodium derivative by hydrogen displacement, as such reactivity might have been expected at the α-carbon of a phosphine oxide. This reaction, however, failed to take place.

In a search for other routes to the dioxides with $x = 1$ we were able to obtain a modest yield of the desired material by the following reaction:

$$2R_2P(O)\cdot MgX + CH_2I_2 \longrightarrow R_2P(O)\cdot CH_2\cdot P(O)R_2 + 2MgXI$$

but an attempt at a similar reaction with the sodium derivative of secondary phosphine oxides proved fruitless.

Finally, it was felt that our previous failures to isolate dialkylchloromethylphosphine oxides from the reactions shown above might have been caused by unusual sensitivity of the product to temperature. Accordingly we allowed a deficient amount of organometallic reagents (lithium or magnesium) to react with chloromethylphosphonic dichloride, so that the reaction mixtures could have been expected to contain some $R_2P(O)\cdot CH_2Cl$, after the reaction of the expectedly more reactive acid chloride units. Treatment of such a reaction mixture with the Grignard reagent from a secondary phosphine oxide, *viz.*, $R_2P(O)\cdot MgX$, indeed afforded a low yield of the desired diphosphine dioxide with $x = 1$. Again, the use of the sodium salt of the secondary phosphine oxide had a negative conclusion.

Two final negative results might be mentioned from our search for routes to the dioxides with $x = 1$. Oxidative chlorophosphonation of trimethylphosphine oxide, with oxygen and phosphorus trichloride, failed to take place after many trials. An Arbuzov reaction between methylene iodide and butyl dibutylphosphinite also failed to take place.

The seven diphosphine dioxides prepared in this group were then examined as to their tendency to form associated aggregates. Molecular-weight determinations, made ebullioscopically in benzene or in acetone (the latter being necessitated by insolubility of some members in the hydrocarbon solvent), showed that all but two of the phosphine dioxides were substantially monomeric in solution. Methylated members with $x = 2$ and 3 were dimeric and trimeric, respectively. It appeared therefore that the nature of the radicals at the phosphorus atom is of a greater influence on the association of these compounds than is the length of the polymethylene bridge between the phosphorus atoms.

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Experimental

The details of numerous unsuccessful trials are omitted, as these experiments employed conventional techniques.

Tetra-P-*phenyltrimethylenediphosphine Dioxide*.—Trimethylene ditoluene-*p*-sulphonate, m. p. 91—93° (15 g., 0·039 mole), in dry benzene (300 ml.) was added to the Grignard reagent from bromobenzene and magnesium (36·4 g.) and diethyl hydrogen phosphonate acid (69 g.) in ether. The ether component of the solvent mixture was replaced by benzene, and the mixture was refluxed for 44 hr., after which a solution of potassium hydroxide (180 g.) in ethanol (1 l.) was added and the precipitated magnesium hydroxide was separated. The filtrate was combined with ethanolic washings of the filter-cake, and the total filtrate was concentrated *in vacuo*. The residue was taken up in benzene and washed with aqueous potassium hydroxide. Distillation of the organic solution gave the desired *dioxide* (5 g., 36%), b. p. 295—300°/0·1 mm. After several weeks in ethanol–hexane solution, the product crystallized in plates, m. p. 195—196° after two recrystallizations from the same solvent [Found: P, 13·9, 14·1%; *M* (in benzene), 453. $C_{27}H_{26}O_2P_2$ requires P, 13·9%; *M*, 444].

The same dioxide was formed in a somewhat lower yield when trimethylene bromide was used instead of the disulphonate. The crude product contained bromine, evidently owing to a partial reaction; after treatment with alcoholic potassium hydroxide, the product was purified as shown above.

Tetra-P-*phenylethylenediphosphine Dioxide*.—The above procedure with ethylene ditoluene-*p*-sulphonate gave 41% of the desired *dioxide*, which formed plates, m. p. 276—278°, from benzene [Found: P, 14·2%; *M* (in acetone), 415. $C_{26}H_{24}O_2P_2$ requires P, 14·4%; *M*, 430].

Tetra-P-*butyltrimethylenediphosphine Dioxide*.—The above procedure with trimethylene ditoluene-*p*-sulphonate gave 43% of this *dioxide*, which formed needles, m. p. 128—129°, from hexane [Found: P, 16·9, 17·0%; *M* (in benzene), 356. $C_{19}H_{42}O_2P_2$ requires 17·0%; *M*, 364]. Only a trace of this material was formed after a 24-hr. reaction of an excess of butylmagnesium bromide and tetraethyl trimethylenediphosphonate in boiling dipentyl ether.

In an alternate procedure, tetraethyl trimethylenediphosphonate (91 g.) in dry benzene (50 ml.) was added to phosphorus pentachloride (240 g., 4 mol.) in refluxing benzene, and the mixture was boiled overnight during which ~50% of the theoretical volume of ethyl chloride was collected in a chilled trap connected to the reflux condenser. The volatile materials were removed under water-pump vacuum and the viscous dark residue was suspended in benzene (300 ml.) and added to a Grignard reagent prepared from butyl bromide (192 g.). The whole was refluxed overnight and worked up as described above; some 20 g. of crude neutral product were obtained. This distilled mainly at 193—195°/0·07 mm. (the distillation was stopped before completion by incipient decomposition). In all, only 4·0 g. of the dioxide were obtained pure by this procedure.

Tetra-P-*butylethylenediphosphine Dioxide*.—(*a*) The above procedure, with ethylene ditoluene-*p*-sulphonate and the Grignard reagent from butylmagnesium bromide and diethyl hydrogen phosphonate gave 40% of this *dioxide*, b. p. 222—224°/0·8 mm., m. p. 174—175° (from benzene–ether) [Found: P, 17·6%; *M* (in benzene), 351. $C_{18}H_{40}O_2P_2$ requires P, 17·7%; *M*, 350]. This dioxide showed a tendency to dissociate or disproportionate: vacuum-sublimation of a sample gave a series of fractions in which the m. p. dropped progressively with time, beginning with the m. p. shown above. The residual material after several hours' heating in the sublimation apparatus was a semisolid, apparently polymeric mass, while the sublimate contained detectable amounts of tributylphosphine oxide.

(*b*) Tetraethyl ethylenediphosphonate (70 g., 0·232 mole) was added during 1 hr. to phosphorus pentachloride (222 g., 1·065 moles) in benzene (500 ml.), and the mixture was refluxed overnight, during which ~60% of the calculated volume of ethyl chloride was collected. The cooled mixture was treated with sulphur dioxide to destroy the residual pentachloride, and the whole was concentrated *in vacuo*. The residual viscous liquid failed to crystallize, and was treated with additional phosphorus pentachloride (29·2 g., 0·14 mole) in chlorobenzene (150 ml.). After treatment with sulphur dioxide and concentration, the mixture gave a product which melted at 195—205° with much decomposition. This material contained Cl, 54·3% and P, 23·6% (calc. for ethylenebisphosphonic tetrachloride 53·7 and 23·5%, respectively). It was added to butylmagnesium bromide prepared from magnesium (33 g., 46% excess), and the

whole was refluxed in dipropyl ether for 12 hr. The usual working-up gave 36 g. of a crude product, which after a vacuum-distillation and purification gave only 1 g. of the above dioxide.

Tetra-P-*butylmethylenediphosphine Dioxide*.—Chloromethylphosphonic dichloride (41·9 g., 0·25 mole) was treated at −5° with butylmagnesium bromide (from 12·2 g. of magnesium). After having been stirred overnight, the crude mixture was added during 1·5 hr. to a mixture prepared from magnesium (24·3 g.), butyl bromide (142 g.), and diethyl hydrogen phosphonate (46 g.) in ethyl ether. The whole was refluxed with stirring for 24 hr. after which it was worked up as described above. Only 120 mg. of the above *dioxide* were isolated; they formed needles, m. p. 172—174° from hexane [Found: P, 19·5%; *M* (in benzene), 340. $C_{17}H_{38}O_2P_2$ requires P, 19·7%; *M*, 336].

In a similar reaction the necessary Grignard reagent of dibutylphosphine oxide was prepared from an isolated phosphine oxide by treatment of it with ethylmagnesium bromide. The reaction run with 0·2-molar amounts of reactants gave 170 mg. (0·25%) of the dioxide, m. p. 167—170°. After sublimation under a high vacuum and recrystallization, ~77 mg. of the dioxide, m. p. 174—176°, were isolated.

Tetra-P-*methyltrimethylenediphosphine Dioxide*.—The above scheme with trimethylene ditoluene-*p*-sulphonate, methylmagnesium iodide, and diethyl hydrogen phosphonate gave 23·5% of this *dioxide*, m. p. 211—212° after vacuum-sublimation [Found: P, 31·5, 31·5%; *M* (in acetone), 337. $C_7H_{18}O_2P_2$ requires P, 31·6%; *M*, 196]. This dioxide was reported earlier [5] to be a semiliquid substance.

Tetra-P-*methylethylenediphosphine Dioxide*.—To phosphorus pentachloride (117 g., 0·56 mole) was added phosphorus oxychloride (450 g.) and the mixture was treated during 30 min. with tetraisopropyl ethylenediphosphonate (50 g., 0·14 mole). After 10 hours' refluxing during which only 23 ml. of isopropyl chloride were evolved, the mass was treated with sulphur dioxide and was cooled overnight, yielding a precipitate. This was stirred with warm toluene, part of which was then distilled off along with residual phosphorus oxychloride, and the residue was chilled, yielding an apparent tetrachloride (33 g., 89%), decomp. 155—165° (see ref. 3). This material was refluxed for 42 hr. with methylmagnesium iodide (8 moles) in ether and after the usual working-up gave 2·6 g. of neutral product. Sublimation at 190°/0·1 mm. gave a product (2·3 g.), m. p. 275—280°. This material was acidic and was, accordingly, made strongly alkaline with potassium hydroxide solution, evaporated, and sublimed *in vacuo*, yielding but 20 mg. of *dioxide*, m. p. 232—233° [Found: P, 34·0, 34·2%; *M* (in acetone), 532. $C_6H_{16}O_2P_2$ requires P, 34·0%; *M*, 182].

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Ross Chemical Laboratory, Auburn University,
Auburn, Alabama, U.S.A. [*Received, December 22nd*, 1960.]

[5] Grayson, Keough, and Johnson, *J. Amer. Chem. Soc.*, 1958, **81**, 4803.

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470. *Thiocyanogen Chloride. Part IV.*[1] *Reaction with Aromatic Hydrocarbons; Heterolytic and Homolytic Substitution in Benzene Homologues.*

By R. G. R. Bacon and R. G. Guy.

In an organic solvent and with no added catalyst, thiocyanogen chloride effects nuclear thiocyanation in a much wider range of aromatic hydrocarbons than does thiocyanogen. Reactions between thiocyanogen chloride and *m*-xylene, higher benzene homologues, naphthalene, and anthracene are described. The relative rates of nuclear thiocyanation of the hydrocarbons are in the same order as their relative rates of nuclear substitution by molecular halogens. With ultraviolet irradiation, homolytic reaction occurs between thiocyanogen chloride and arylalkyl hydrocarbons, the result being replacement of an α-hydrogen atom by the SCN group. This reaction is described for toluene, ethylbenzene, *m*-xylene, isopropylbenzene, diphenylmethane, and triphenylmethane; the three last-named hydrocarbons give an isothiocyanate instead of a thiocyanate. Polar effects in the hydrocarbon, assisted by a polar solvent, may successfully compete with the effect of light; *e.g.*, with irradiated solutions of thiocyanogen chloride in acetic acid, thiocyanation occurs partly in the nucleus of *m*-xylene and wholly in the nucleus of mesitylene.

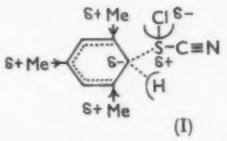
The nuclear thiocyanation of phenols, amines, and their derivatives by thiocyanogen chloride was described in earlier papers.[1,2] These reactions have similar characteristics to the heterolytic substitutions which an activated aromatic nucleus undergoes with molecular halogens or interhalogen compounds.[3] When aromatic hydrocarbons react with thiocyanogen chloride, two effects are possible, and these are likewise analogous to the results of halogenations of the hydrocarbons: nuclear thiocyanation may occur, by a presumed heterolytic mechanism; or side-chain thiocyanation may occur, by a homolytic mechanism, if the compound possesses an alkyl substituent containing at least one α-hydrogen atom. The latter type of substitution provides the first example of a reaction involving homolysis of the Cl–S bond of thiocyanogen chloride.[4] Its easy occurrence was first noticed while we were examining the thiocyanation of 1-methylnaphthalene, details of which are given in Part V (following paper). The present paper concerns twelve other aromatic hydrocarbons, mainly homologues of benzene.

Nuclear Thiocyanation.—For halogens and interhalogen compounds, the known order of reactivity[3] towards an aromatic nucleus is: $Cl_2 > BrCl > Br_2 > ICl > I_2$. Thiocyanogen, $(SCN)_2$, fits into this series between iodine chloride and iodine, while thiocyanogen chloride, NCS·Cl, occupies approximately the same position as iodine chloride. The rate curves shown in Fig. 1 illustrate nuclear substitution by some of these reagents in a fairly reactive hydrocarbon, 1-methylnaphthalene; 50% of monosubstitution was reached with both thiocyanogen chloride and iodine chloride in about 3 hr., and with bromine in about 1 min., while chlorine entered even more rapidly into disubstitution.

The only aromatic hydrocarbons known to undergo uncatalysed nuclear substitution by thiocyanogen are anthracene and some larger polycyclic compounds.[5] Söderbäck found that the reactivity of thiocyanogen is greatly enhanced by Friedel–Crafts catalysts, which lead to ready substitution even in benzene;[6] there seems to have been no

[1] Part III, Bacon and Guy, *J.*, 1960, 318.
[2] Angus and Bacon, *J.*, 1958, 774; Bacon and Irwin, *J.*, 1958, 778.
[3] de la Mare and Ridd, "Aromatic Substitution. Nitration and Halogenation," Butterworths, London, 1959.
[4] Bacon, Guy, Irwin, and Robinson, *Proc. Chem. Soc.*, 1959, 304.
[5] Wood and Fieser, *J. Amer. Chem. Soc.*, 1941, **63**, 2323.
[6] Söderbäck, *Acta Chem. Scand.*, 1954, **8**, 1851.

subsequent study of this method of thiocyanation. Without the aid of a catalyst, thiocyanogen chloride causes thiocyanation of a wider range of aromatic hydrocarbons than does thiocyanogen under similar conditions: $ArH + Cl{\cdot}SCN \longrightarrow Ar{\cdot}SCN + HCl$. The greater reactivity of the chloride is attributed to polarisation of the Cl–SCN bond.[2] We have not yet explored the effect of catalysts on this reaction. By analogy with a mechanism postulated for aromatic substitutions effected by molecular halogens,[3] nuclear thiocyanation may be considered to involve heterolysis of a Cl–S bond, perhaps aided by associated molecules of solvent or catalyst, in a transition-state complex, such as that shown (I) for mesitylene and thiocyanogen chloride. Among hydrocarbons so far examined with the reagent, only anthracene (see below) has given evidence that chlorine may also enter the molecule. Results of nuclear thiocyanation by thiocyanogen chloride are shown in Table 1 and Fig. 2.



(I)

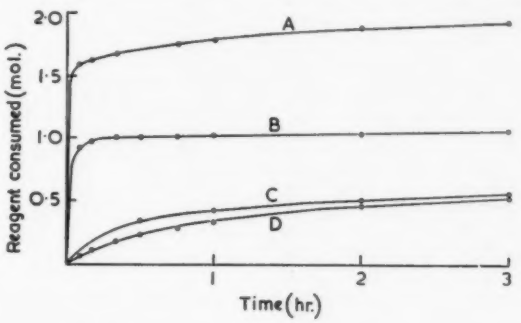


FIG. 1. *Reaction of* 1-*methylnaphthalene* (1 *mol.*) *in acetic acid in darkness at* 20° *with the reagents* (2 *mol.*): 0·151M-Cl_2 (A), 0·167M-Br_2 (B), 0·161M-Cl·SCN (C), 0·158M-ICl (D).

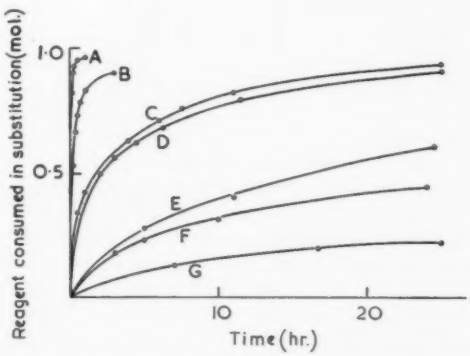


FIG. 2. *Substitution of pentamethylbenzene* (A), *mesitylene* (*exp.* i) (B), 1-*methylnaphthalene* (C), 2-*methylnaphthalene* (D), m-*xylene* (*at* 40°) (E), *durene* (F), *and naphthalene* (G) *by* Cl·SCN *at* 20° *under the conditions given in Table* 1.

Reactions were usually carried out in darkness because of the possible occurrence of some side-chain thiocyanation in daylight (cf. Part V). The solvent, acetic acid, is known to be a good medium for nuclear halogenations [3] and it had previously been found suitable for thiocyanation of anilides and phenolic ethers.[1] If a hydrocarbon fails to undergo substitution at 20—40°, success is unlikely at higher temperatures, since the spontaneous decomposition of the reagent will then be correspondingly rapid. Experiments (i), (ii), and (iii) with naphthalene illustrate the effect of temperature for a hydrocarbon of rather low reactivity towards thiocyanogen chloride. The reagent was customarily used in 100% excess, partly to increase the rate of substitution and partly to allow for some loss by spontaneous decomposition. Experiments (i), (ii), and (iii) with mesitylene illustrate the effect of varying the concentration of reagent. Its decomposition is usually very much slower than its reaction with a hydrocarbon, but an approximate allowance was made for

it, as previously described,[1] when rates of substitution were recorded. Reactions beyond the monothiocyanation stage were not observed.

In the monocyclic series of hydrocarbons, the presence of two or more methyl groups, *ortho* or *para* to the point of substitution, activates the nucleus sufficiently for reaction to occur with thiocyanogen chloride, while in the polycyclic series reactivity extends down to unsubstituted naphthalene. Relative reactivities are compared in Table 1 with those reported for bromination of the hydrocarbons by molecular bromine.[3] The close correspondence observed in the order of reactivity indicates that the thiocyanations and brominations respond similarly to the polar influences which operate in the aromatic hydrocarbons. A similar conclusion was reached for phenols, amines, and their derivatives.[1] The higher rate of catalysed thiocyanation is shown by the fact that with ~0·7M-solutions of thiocyanogen, and with aluminium chloride present, Söderbäck[6] observed complete consumption of the reagent within 0·5 hr., for both mesitylene and naphthalene (cf. Table 1), at or below room temperature.

TABLE 1. *Reaction between hydrocarbons* (1 *mol.*) *and thiocyanogen chloride* (2 *mol.*) *in darkness in acetic acid* (500 *ml.*).

Hydrocarbon	Cl·SCN (M)	Temp.	Time [b] for 50% substn. (hr.)	Relative rates [c] of bromination	Total time (hr.)	Total Cl·SCN consumed (mol.)	Yield of substn. product (mol.)
Toluene	0·150	40°	—	$6·05 \times 10^2$	72	1·66	Nil
m-Xylene	0·154	,,	17	$5·14 \times 10^5$	24	1·46	0·60
Durene	0·156	20	32	$2·83 \times 10^6$	72	1·16	0·67
Mesitylene (i)	0·154	,,	0·2	$1·89 \times 10^8$	3	1·08	0·90
(ii) [a]	0·098	,,	0·3		6	1·08	0·91
(iii) [a]	0·049 [d]	,,	4·0		20	0·81	0·56
Pentamethylbenzene	0·154	,,	<0·1	$8·1 \times 10^8$	1	1·06	0·96
Naphthalene (i) [a]	0·177	60	—	1×10^5	11	1·96	0·20
(ii) [a]	0·183	40	~50		34	1·60	0·37
(iii) [a]	0·191	20	>120		117	1·16	0·42
2-Methylnaphthalene	0·157	,,	2·0		34	1·14	0·81
1-Methylnaphthalene	0·161	,,	1·7		25	1·12	0·92
Anthracene [a]	0·155 [e]	,,	~0·1		5	1·10	0·76

[a] Reaction in daylight. [b] From rate curves (cf. Fig. 2). [c] Data from ref. 3, pp. 137, 173; they are for Br_2 in AcOH, relative to $C_6H_6 = 1$. [d] 1 Mol. used. [e] 1·11 Mol. used.

The product from thiocyanogen chloride and *m*-xylene was a liquid, shown to be 2,4-dimethyl-1-thiocyanatobenzene by an alternative preparation from diazotised 2,4-dimethylaniline. The identity of the products was shown by their physical constants and infrared absorption spectra, and by identification of the thiol obtained on reduction of the thiocyanate group[7] with lithium aluminium hydride. The product from mesitylene had the same m. p. as that described by Söderbäck[6] and was identical with a sample prepared from diazotised mesidine. The structures of the crystalline thiocyanates obtained from durene and pentamethylbenzene are unambiguous and alternative methods of preparation were not carried out. They showed the strong, sharp infrared absorption peak at 2160 $cm.^{-1}$ characteristic of thiocyanates.[8] Like other nuclear aromatic thiocyanates, they were unaffected by ethanolic silver nitrate, whereas the compounds with an α-thiocyanato-group in the side chain (see below) gave a precipitate readily.

Thiocyanogen chloride and naphthalene gave a single product, which was the known 1-thiocyanatonaphthalene, alternatively prepared from 1-naphthylamine. The reaction with anthracene was not so simple. Wood and Fieser treated this hydrocarbon in carbon tetrachloride with 1 or 4·4 mol. of thiocyanogen and in each case obtained 9,10-dithiocyanatoanthracene.[5] Under our conditions, slightly more than 1 mol. of thiocyanogen

[7] Strating and Backer, *Rec. Trav. chim.*, 1950, **69**, 638.

[8] Luskin, Gantert, and Craig, *J. Amer. Chem. Soc.*, 1956, **78**, 4965; Caldow and Thompson, *Spectrochim. Acta*, 1958, **13**, 212; Lieber, Rao, and Ramchandran, *ibid.*, 1959, **13**, 296; Ham and Willis, *ibid.*, 1960, **16**, 279, 393; Svatek, Zahradnik, and Kjaer, *Acta Chem. Scand.*, 1959, **13**, 442.

chloride yielded a monosubstitution product (76%), m. p. 190°, presumably a purer sample of the 9-thiocyanatoanthracene, m. p. 181°, recorded in the literature.[9] The same compound resulted when larger proportions of the reagent were used, and it was then accompanied by substantial mixed fractions of undetermined composition. In one case, a by-product (7%) gave an analysis corresponding to that of a chlorothiocyanatoanthracene. It is well known that addition and elimination at the 9- and 10-positions complicate the substitution of anthracene by electrophilic reagents, and its reaction with thiocyanogen chloride needs further investigation from this point of view.

Thiocyanation in a Substituent Alkyl Group.—Whereas toluene gave no nuclear thiocyanate on prolonged treatment with thiocyanogen chloride in acetic acid at 40°, ultraviolet irradiation of the solution resulted in ready conversion of the hydrocarbon into benzyl thiocyanate. Thiocyanogen chloride absorbs light[2] from 450 to <280 mμ. The light source was a 250 w mercury-vapour lamp, the energy emitted from which included strong radiations at 365 and 436 mμ, and weaker radiations at 302, 313, 334, and 405 mμ. This novel homolytic reaction was applied to other arylalkyl hydrocarbons, in acetic acid or carbon tetrachloride solution, and some results of these experiments are shown in Table 2. As expected, t-butylbenzene failed to react, since it lacks an α-hydrogen atom. In the cases of the other hydrocarbons, entry of the substituent at the α-carbon atom was proved by comparing the products with those obtained by reaction of the corresponding α-chloro- or α-bromo-compounds with thiocyanate ion.

TABLE 2. *Substitution of hydrocarbons by thiocyanogen chloride under ultraviolet irradiation.*

Hydrocarbon (mol.)		Cl·SCN (1 mol.) (molar concn.)	Solvent	Irradiation [a] at 35—45° (hr.)	Total Cl·SCN consumed (mol.)	Product isolated (mol.)
Toluene	(5)	0·154	AcOH	3	0·95	$PhCH_2$·SCN (0·63)
Ethylbenzene	,,	0·166	,,	2	0·97	PhCHMe·SCN (0·68)
Isopropylbenzene ...	,,	0·178	,,	,,	1·00	$PhCMe_2$·NCS (0·13) [b]
t-Butylbenzene [c] ...	,,	0·1	CCl_4	,,		Nil
m-Xylene (i)	,,	0·143	,,	,,	0·96	*m*-C_6H_4Me·CH_2·SCN (I) (0·69)
(ii)	,,	0·144	AcOH	,,	0·87	(I) (0·34) + 2,4,1-$C_6H_3Me_2$·SCN (II) (0·16)
(iii)	(0·5)	0·158	,,	,,	0·43	(I) (0·125) + (II) (0·050)
(iv)	,,	0·143	,,	,, [d]	0·96	(I) (0·18) + (II) (0·025)
Mesitylene	,,	0·152	,,	1	0·43	2,4,6,1-$C_6H_2Me_3$·SCN (0·23)
Diphenylmethane [c]	(5)	0·093	CCl_4	4	0·75	$CHPh_2$·NCS (0·09)
Triphenylmethane [c]	(0·9)	0·119	,,	1	0·92	CPh_3·NCS (0·64)

[a] The temperature is the result of thermal radiation from the lamp, modified by cooling. [b] Losses by decomposition occurred during isolation. [c] Experiments by R. S. Irwin, who also prepared these isothiocyanates with thiocyanogen (see text). [d] No cooling; the temperature rose to 95°.

By adapting the usual chain mechanism used to represent homolytic side-chain halogenation, a reaction sequence may be written:

$$Cl{\cdot}SCN \xrightarrow{h\nu} Cl{\cdot} + {\cdot}SCN$$

$$Ar{-}\overset{|}{C}{-}H + Cl{\cdot}\ (\text{or } {\cdot}SCN) \longrightarrow Ar{-}\overset{|}{C}{\cdot} + HCl\ (\text{or } HSCN)$$

$$Ar{-}\overset{|}{C}{\cdot} + Cl{\cdot}SCN \longrightarrow Ar{-}\overset{|}{C}{-}SCN + Cl{\cdot}\ \text{etc.}$$

The most important feature in this sequence is the formation of a thiocyanate, and not a chloride, in the third step; the arylalkyl radical pairs with SCN, the more electropositive partner, in the fission of the Cl–SCN bond. This recalls Speier's observation that the substitution of toluene by bromine chloride under ultraviolet irradiation gives benzyl

[9] Footner and Smiles, *J.*, 1925, **127**, 2887.

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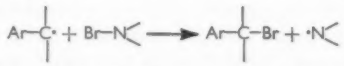
bromide.[10] Walling has commented [11] that our present knowledge of the behaviour of radicals provides no obvious explanation of why the product obtained by Speier should be a bromide rather than a chloride. Further studies of homolytic substitutions by bromine chloride and similar mixed-halogen or halogen–pseudohalogen compounds would be valuable, though the course of such reactions might be complicated by the existence of inter-halogen equilibria, *e.g.*, of the type $A_2 + B_2 \rightleftharpoons 2AB$, which does not occur in solutions of thiocyanogen chloride. A reaction which is very appropriate for comparison with that of thiocyanogen chloride is the well-known side-chain bromination of arylalkyl hydrocarbons by *N*-bromosuccinimide, which is generally interpreted [11] as a homolytic chain reaction involving the step:



Here too the arylalkyl radical pairs with the more electropositive partner in the fission of the Br–N< bond.

The reactions of thiocyanogen chloride solutions with *m*-xylene and with mesitylene, shown in Table 2, deserve comment, since they demonstrate that the reactants are rather delicately poised between side-chain substitution, promoted by the irradiation, and nuclear substitution, promoted by a polar solvent and by polar influences from the alkyl groups. Thus, when acetic acid is the solvent, thiocyanation occurs partly in the nucleus of *m*-xylene and entirely in the nucleus of mesitylene, in spite of irradiation. In general, reaction in acetic acid in darkness is the preferred means of nuclear substitution, while reaction in carbon tetrachloride under ultraviolet irradiation is the preferred means of side-chain substitution.

Another feature of Table 2 is that the product isolated may be an isothiocyanate instead of a thiocyanate. In certain cases (observations by R. S. Irwin) the isothiocyanate may be the only detectable product, as in the reaction with triphenylmethane, while in other cases, as with isopropylbenzene or diphenylmethane, it may be formed through the isomerisation, R·S·C:N ⟶ R·N:C:S, of a thermally labile thiocyanate which is detectable as the initial product. Further information on the formation and structure of side-chain thiocyanation products has become available from later investigations.[12] Thiocyanates and isothiocyanates may be reliably and rapidly distinguished by their infrared absorption spectra.[8] For example, the spectrum of 1′-thiocyanatoethylbenzene showed a sharp peak at 2160 cm.$^{-1}$, characteristic of all the nuclear and side-chain thiocyanates examined, while the spectrum of distilled samples of 2-isothiocyanato-2-phenylpropane showed a strong and broad band at 2100 cm.$^{-1}$, with a shoulder at ~2000 cm.$^{-1}$, characteristic of isothiocyanates; in spectra of a sample of the ethylbenzene derivative which had been partially isomerised at 150°, or of a sample of the isopropylbenzene derivative before distillation, the band at 2100 cm.$^{-1}$ was dominant, but the peak at 2160 cm.$^{-1}$ was also clearly present.

Experimental

Thiocyanations of the Aromatic Nucleus.—Solutions of thiocyanogen chloride in acetic acid were prepared as described in Part III.[1] Thiocyanations of hydrocarbons and the recording of reaction rates were carried out as described for ethers and anilides in the same paper. Reaction flasks were usually rendered opaque with black paint. At the end of a thiocyanation, lead chloride (from the preparation of the reagent) was filtered off and the product was isolated by dilution of the solution with ice and water, followed, where necessary, by extraction with an organic solvent. To discover isomers or by-products, the isolated material was dissolved in light petroleum and chromatographed on a column of silica gel; 20—70 fractions, each of

[10] Speier, *J. Amer. Chem. Soc.*, 1951, **73**, 826.
[11] Walling, "Free Radicals in Solution," Wiley and Sons, New York, 1957.
[12] Bacon, Guy, and Irwin; and Bacon and Irwin, following papers.

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volume ~70 ml., were collected. The following details refer to experiments summarised in Table 1.

Toluene. After treatment of toluene (3·40 g.) with the reagent, as shown in the Table, and removal of solvents, there remained an orange gum (0·97 g.) from which nothing could be separated by chromatography with light petroleum or benzene (cf. *m*-xylene).

m-*Xylene.* Under the conditions given in Table 1, 4·09 g. of *m*-xylene yielded 4·67 g. of a brown oil, which was chromatographed with benzene–light petroleum (3 : 7). Out of 40 fractions, nos. 7—25 yielded 2,4-*dimethyl*-1-*thiocyanatobenzene* (3·78 g., 60%), b. p. 133—134°/12 mm., n_D^{25} 1·5610 (Found: C, 66·4; H, 5·85; N, 8·4; S, 19·55. C_9H_9NS requires C, 66·25; H, 5·55; N, 8·6; S, 19·6%). A sample (1·0 g.) was reduced by treatment in ether (25 ml.) with lithium aluminium hydride (1·2 mol.).[7] When the vigorous reaction had subsided, the product was treated with water and then with 2N-sulphuric acid; the ether layer was evaporated, and the residual thiol was dissolved in ethanol, treated with 10% aqueous sodium hydroxide, and added to 1-chloro-2,4-dinitrobenzene (1·0 g.) in ethanol. The yellow precipitate was redissolved by warming, and sodium chloride was filtered off. On cooling, 2,4-*dimethylphenyl* 2,4-*dinitrophenyl sulphide* crystallised in yellow needles, m. p. 139—140° (Found: C, 55·4; H, 3·85; N, 9·2; S, 10·3. $C_{14}H_{12}N_2O_4S$ requires C, 55·25; H, 4·0; N, 9·2; S, 10·5%).

For comparison, 2,4-dimethylaniline (0·1 mole) was dissolved in sulphuric acid (0·3 mole) and water (150 ml.) and diazotised. The ice-cold diazonium salt solution was added during 10 min. to a stirred ice-cold solution of potassium thiocyanate (0·5 mole) and ferric chloride (0·15 mole) in water (100 ml.). After being stirred for 2 hr. at 0° and 20 hr. at room temperature, the thick black suspension was kept for 1 hr. at 40°, which caused rapid evolution of nitrogen. Extraction, distillation, and further purification by chromatography yielded 2,4-dimethyl-1-thiocyanatobenzene (53%), b. p. 131—132°/10 mm., n_D^{25} 1·5610. It was reduced and the resulting thiol converted into 2,4-dimethylphenyl 2,4-dinitrophenyl sulphide, m. p. 139—140°, not depressed by admixture with the sample described above.

Durene. Under the conditions given in Table 1, 5·18 g. of durene yielded part of the product (2·42 g., 33%) as a pale yellow precipitate, m. p. 46—49°, when the solution was diluted. Recrystallisation from ethanol gave pure 2,3,5,6-*tetramethyl*-1-*thiocyanatobenzene*, m. p. 49—50° (Found: C, 69·25; H, 6·8; N, 7·25; S, 16·8. $C_{11}H_{13}NS$ requires C, 69·1; H, 6·85; N, 7·35; S, 16·7%). A brown oil (3·36 g.) was obtained by ether-extraction of the diluted solution. The only product which this yielded when chromatographed with 1 : 1 benzene–light petroleum was additional 2,3,5,6-tetramethyl-1-thiocyanatobenzene (2·50 g., 34%).

Mesitylene. Under the conditions given for experiment (i) with mesitylene in Table 1, 4·58 g. of the hydrocarbon yielded practically pure 2,4,6-trimethyl-1-thiocyanatobenzene (6·10 g., 90%), m. p. 70—72°, when the solution was diluted. Recrystallisation from ethanol yielded the thiocyanate in needles, m. p. 71—72° (lit.,[6] 71—72°) (Found: C, 67·6; H, 6·25; N, 7·85; S, 18·6. Calc. for $C_{10}H_{11}NS$: C, 67·8; H, 6·25; N, 7·9; S, 18·1%). For comparison, nitromesitylene was reduced [13] to mesidine (78%), which was diazotised and treated with ferric thiocyanate as described for 2,4-dimethylaniline. After the evolution of nitrogen, the suspended solid was extracted into ether and the product (70%) was purified by chromatography and recrystallisation to give 2,4,6-trimethyl-1-thiocyanatobenzene, m. p. 71—72°, not depressed on admixture with the sample described above.

Pentamethylbenzene. Under the conditions given in Table 1, 5·71 g. of the hydrocarbon yielded the practically pure thiocyanate (7·61 g., 96%), m. p. 83—86°, on dilution of the solution. Recrystallisation from ethanol gave colourless prisms of *pentamethylthiocyanatobenzene*, m. p. 85—86° (Found: C, 70·1; H, 7·2; N, 6·7; S, 15·35. $C_{12}H_{15}NS$ requires C, 70·2; H, 7·35; N, 6·8; S, 15·6%).

Naphthalene. Under the conditions given for experiment (i) with naphthalene in Table 1, 5·74 g. of the hydrocarbon yielded a crude product (6·26 g.) on dilution of the solution. Chromatography with 1 : 1 benzene–light petroleum gave unchanged naphthalene (1·85 g.), followed, in fractions nos. 6—17, by 1-thiocyanatonaphthalene (3·46 g., 42%), which, when recrystallised from ethanol, showed m. p. 54·5—55·5° (lit.,[14] 55°) (Found: C, 71·65; H, 3·65; N, 7·6; S, 17·25. Calc. for $C_{11}H_7NS$: C, 71·35; H, 3·8; N, 7·55; S, 17·3%). For comparison, it was prepared (62%) from 1-naphthylamine, by the procedure given for 2,4-dimethylaniline, and extracted into benzene. Purification by steam-distillation or chromatography, followed by

[13] Fierz-David and Mannhart, *Helv. Chim. Acta*, 1937, **20**, 1024.
[14] Challenger and Wilkinson, *J.*, 1922, **121**, 100.

recrystallisation from ethanol, gave 1-thiocyanatonaphthalene, m. p. 54·5—55·5°, not depressed on admixture with the sample described above.

Anthracene. Under the conditions given in Table 1, the anthracene (11·73 g.) dissolved slowly when added to the stirred acetic acid solution of thiocyanogen chloride, and a bright yellow crystalline precipitate rapidly separated. After filtration, this was extracted with hot acetone, evaporation of which left fairly pure 9-thiocyanatoanthracene (11·70 g., 76%), m. p. 182—187°, giving bright yellow needles, m. p. 189—190° (lit.,[9] 181°) on recrystallisation from acetone (Found: C, 76·4; H, 4·05; N, 6·05; S, 13·45. Calc. for $C_{15}H_9NS$: C, 76·6; H, 3·85; N, 5·95; S, 13·6%). Dilution of the filtered acetic acid solution with water gave a mixed, lower-melting product, difficult to purify.

Reaction was also carried out at 20° with 0·155M-thiocyanogen chloride (4 mol.). Titration showed the disappearance of 1·03 mol. of reagent in 10 min., and 2·01 mol. in 50 hr.; in a similar preparation at 40°, 3·04 mol. of reagent disappeared in 24 hr. As before, pure product was obtained only from the insoluble portion (2·87 g. from 3·24 g. of anthracene). Fractional crystallisation of this from acetone gave 9-thiocyanatoanthracene (0·96 g., 22%), m. p. and mixed m. p. 188—190°, and (probably) 9-*chloro*-10-*thiocyanatoanthracene* (0·36 g., 7%), m. p. 218—219° (Found: C, 66·6; H, 3·05; Cl, 13·0; N, 5·35; S, 12·15. $C_{15}H_8ClNS$ requires C, 66·75; H, 3·0; Cl, 13·15; N, 5·2; S, 11·85%). Chromatography did not appear to be superior to recrystallisation for purification of the products.

Thiocyanation with Ultraviolet Irradiation.—Reactions were carried out (see Table 2) in gently stirred solutions in a Pyrex flask placed 8 cm. from a 250 w " Mazda " ME/D box-type mercury-vapour lamp. A water-cooled tube inside the flask counteracted the effect of thermal radiation from the lamp and kept the temperature of the solution at ~40°. The procedure was otherwise the same as that described above when acetic acid was the solvent. When reaction was to be carried out in carbon tetrachloride, thiocyanogen chloride was prepared by mixing solutions of chlorine and thiocyanogen in this solvent.[3] When the reaction was terminated, the solution was shaken with water to decompose and remove unchanged reagent, and the carbon tetrachloride was evaporated.

Toluene. Reaction with thiocyanogen chloride was carried out under the conditions given in Table 2. The solution was diluted with water and extracted with ether; solvent was evaporated, and the solid residue was chromatographed on silica gel with 2 : 3 benzene–light petroleum, 35 fractions being collected. Fractions 11—25 yielded benzyl thiocyanate (63%), m. p. 40—41° after recrystallisation from ethanol (lit.,[9] 41°) (Found: C, 64·6; H, 4·9; N, 9·0; S, 21·2. Calc. for C_8H_7NS: C, 64·4; H, 4·75; N, 9·4; S, 21·45%). Apart from a trace of oil (1%), containing no combined chlorine, in fractions 7—10, the column yielded no other product, even when eluted with more polar solvents. In a similar chromatographic treatment of a 1 : 1 mixture of benzyl thiocyanate and benzyl chloride, the latter separated quantitatively in fractions 3—4. The solvent mixture which had been removed from the reaction product was treated with cold aqueous sodium carbonate and fractionally distilled, but no benzyl chloride was found. From a similar solvent mixture, to which benzyl chloride had been added, the chloride was readily thus separated, and was estimated with ethanolic silver nitrate. Treatment of benzyl bromide with ammonium thiocyanate (2 mol.) in refluxing acetone yielded benzyl thiocyanate (95%), m. p. 40—41°, not depressed on admixture with the product obtained with thiocyanogen chloride.

Ethylbenzene. Reaction was carried out under the conditions given in Table 2 and the product was treated as described for toluene. From chromatography with benzene–light petroleum (1 : 1, changing to 7 : 3), 35 fractions were collected. A trace of oil (1%) was obtained from fractions 6 and 7, and 1′-thiocyanatoethylbenzene (68%) from fractions 8—16. On distillation, the latter showed b. p. 136—138°/11 mm. (lit.,[15] 157—159°/36 mm.), n_D^{25} 1·5610, and gave an infrared absorption spectrum identical with that from an authentic sample (see below) (Found: C, 66·4; H, 5·35; N, 8·6; S, 19·4. Calc. for C_9H_9NS: C, 66·25; H, 5·55; N, 8·6; S, 19·6%). By a procedure similar to that described above for 2,4-dimethyl-1-thiocyanatobenzene, the 1′-thiocyanatoethylbenzene was converted into 2,4-dinitrophenyl 1-phenylethyl sulphide, which formed yellow prisms, m. p. 108—109° (lit.,[16] 109—110°) (Found: C, 55·4; H, 4·1; N, 9·15; S, 10·4. Calc. for $C_{14}H_{12}N_2O_4S$: C, 55·25; H, 4·0; N, 9·2; S, 10·5%). For

[15] Wheeler and Johnson, *Amer. Chem. J.*, 1901, **26**, 202.
[16] Behringer, *Annalen*, 1949, **564**, 219.

comparison, 1-phenylethanol was converted into 1′-bromoethylbenzene [17] (83%), and the latter was treated with ammonium thiocyanate (2 mol.) in refluxing acetone for 1 hr. to give 1′-thiocyanatoethylbenzene (94%), which was purified by distillation and chromatography. The pure sample, b. p. 136—138°/11 mm., n_D^{25} 1·5614, was likewise converted into 2,4-dinitrophenyl 1-phenylethyl sulphide, m. p. 108—109°, unchanged on admixture with the sample described above.

Cumene. Reaction carried out under the conditions shown in Table 2 gave a brown oil (91%), which was isolated as described for toluene. It was impure and unstable. When chromatographed on the usual silica-gel column with 1 : 1 benzene–light petroleum, 42% of the product (fractions 1—3) had a hydrocarbon-like odour, only 14% (fractions 7—18) was the desired thiocyanation product, and 27% (fractions 31—34, eluted with benzene–ether) was a viscous red oil. The fractions containing the thiocyanation product varied in refractive index and became deep yellow when kept, but yielded pure 2-*isothiocyanato*-2-*phenylpropane* on fractional distillation (Found: C, 67·8; H, 6·0; S, 18·1. $C_{10}H_{11}NS$ requires C, 67·8; H, 6·25; N, 7·9; S, 18·05%). This was also obtained (b. p. 80°/0·2 mm.) by fractional distillation of the crude product. Alternatively, 2-phenylpropan-2-ol was treated with hydrogen chloride in benzene to give 2-chloro-2-phenylpropane,[18] which, after removal of solvent under reduced pressure, but without distillation, was kept for 3 days at room temperature with ammonium thiocyanate (2 mol.) in acetone. The solution was added to water and extracted with ether; the extract was washed with aqueous sodium hydrogen carbonate and evaporated, and the residue (68% yield) was distilled, to give 2-isothiocyanato-2-phenylpropane, b. p. 51—53°/0·04 mm. (Found: C, 68·1; H, 5·9; N, 7·85; S, 18·1%). Samples from the two sources gave the same infrared absorption spectrum, with a strong, broad band at 2100 cm.$^{-1}$, and each readily gave a precipitate with cold ethanolic silver nitrate.

m-*Xylene.* Under the conditions given for experiment (ii) with *m*-xylene in Table 2, the product, obtained by dilution of the acetic acid solution with water and ether-extraction, was a red-brown oil, which was chromatographed. Fractions 11—19, obtained with 3 : 7 benzene–light petroleum, yielded 2,4-dimethyl-1-thiocyanatobenzene (16%), n_D^{25} 1·5610, identical with that resulting from reaction in darkness (see above). Fractions 25—35, obtained with 3 : 2 benzene–light petroleum, yielded 3-methylbenzyl thiocyanate (36%), b. p. 144—146°/10 mm. (lit.,[15] 147°/12 mm.), n_D^{25} 1·5657 (Found: C, 66·2; H, 5·45; N, 8·6; S, 20·2. Calc. for C_9H_9NS: C, 66·25; H, 5·55; N, 8·6; S, 19·6%). Unlike the nuclear isomer, it readily gave a precipitate with warm ethanolic silver nitrate. Further elution with chloroform only yielded traces of intractable gums. The 3-methylbenzyl thiocyanate was reduced as described above and the resulting thiol was converted into 3-*methylbenzyl* 2,4-*dinitrophenyl sulphide*, which crystallised in yellow needles, m. p. 125—126° (Found: C, 55·6; H, 3·9; N, 9·55; S, 10·55. $C_{14}H_{12}N_2O_4S$ requires C, 55·25; H, 4·0; N, 9·2; S, 10·5%).

For comparison, *m*-xylene (0·9 mole), *N*-bromosuccinimide (0·3 mole), benzoyl peroxide (1 g.), and carbon tetrachloride (100 ml.) were refluxed (7 hr.), giving 3-methylbenzyl bromide (63%), b. p. 103—105°/16 mm. (lit.,[19] 100—101°/14 mm.). This reacted (2 hr.) with ammonium thiocyanate (2 mol.) in boiling ethanol to give 3-methylbenzyl thiocyanate, identical in b. p., n_D^{25}, and infrared absorption spectrum with the sample obtained by thiocyanation. Likewise, it gave the same 2,4-dinitrophenyl sulphide, m. p. and mixed m. p. 125—126°.

Mesitylene. Under the conditions given in Table 2, 4·58 g. of mesitylene gave 4·34 g. (64%) of crude product, m. p. 52—62°, which was chromatographed with 1 : 1 benzene–light petroleum. Fractions 5—11 contained 2,4,6-trimethylphenyl thiocyanate (45%), m. p. 71—72° after one recrystallisation. The only other product (5%) in the chromatogram was a semi-solid from fractions 13—19, which contained more trimethylphenyl thiocyanate, accompanied by a minute amount of an unidentified higher-melting product.

[By R. S. Irwin] *Diphenylmethane.* Reaction with thiocyanogen chloride was carried out at 35° under conditions given in Table 2. Evaporation of solvent under reduced pressure left an impure liquid, in which the presence of a thiocyanate group was shown by a sharp peak at 2169 cm.$^{-1}$ in the infrared absorption spectrum. Removal of excess of diphenylmethane at 74°/0·1 mm., followed by chromatography on silica gel with 1 : 9 benzene–light petroleum, gave diphenylmethyl isothiocyanate (9%), which crystallised from light petroleum in prisms, m. p.

[17] Hughes, Juliusburger, Scott, Topley, and Weiss, *J.*, 1936, 1173.
[18] Hoffmann, *J. Amer. Chem. Soc.*, 1929, **51**, 2546.
[19] Titley, *J.*, 1926, 514.

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57° (lit.,[20] 56·5—57·5°), and gave a strong broad band at 2060 cm.$^{-1}$ in the infrared absorption spectrum. It was identical with the product obtained by thiocyanation of diphenylmethane with thiocyanogen.[4,12]

[By R. S. IRWIN] *Triphenylmethane.* Reaction was carried out with thiocyanogen chloride at 37° under the conditions given in Table 2. The solvent was evaporated and the residue recrystallised from 1 : 1 ethanol–chloroform, to yield triphenylmethyl isothiocyanate (71%) in prisms, m. p. 137°. The sample was identical with that obtained by thiocyanation with thiocyanogen; [4,12] both showed a strong broad band at 2050 cm.$^{-1}$.

We gratefully acknowledge a maintenance grant (to R. G. G.) from Imperial Chemical Industries Limited, Dyestuffs Division.

QUEEN'S UNIVERSITY, BELFAST. [*Received, December 22nd,* 1960.]

[20] Kaye, Kogon, and Parris, *J. Amer. Chem. Soc.*, 1952, **74**, 403.

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471. *Thiocyanogen Chloride. Part V.*[1] *Heterolytic and Homolytic Thiocyanation of Alkylnaphthalenes.*

By R. G. R. BACON, R. G. GUY, and R. S. IRWIN.

The course of thiocyanation of 1-methyl-, 2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-t-butyl-naphthalene by thiocyanogen chloride is attributed to competition between heterolytic substitution of the nucleus, promoted by a polar solvent, and homolytic substitution of an α-hydrogen atom in the alkyl group, promoted by light or a peroxide. Comparisons are made with known results of halogenation of methylnaphthalenes. Thiocyanation of 1-methylnaphthalene in acetic acid in darkness gives only 1-methyl-4-thiocyanatonaphthalene; in irradiated carbon tetrachloride it gives only 1-thiocyanatomethylnaphthalene; in acetic acid in the light it gives both; in carbon tetrachloride in darkness it gives neither. Similarly, in acetic acid in darkness the 2-alkylnaphthalenes give 2-alkyl-1-thiocyanatonaphthalenes; in irradiated carbon tetrachloride, 2-methyl- and 2-ethyl-naphthalene give the α-thiocyanato-derivatives, 2-isopropylnaphthalene gives the α-isothiocyanato-derivative, and 2-t-butylnaphthalene does not react. Structures of products are proved by alternative methods of synthesis, by infrared spectral characteristics, by reduction, and by other reactions. Mobility of the thiocyanato-group in 2-1′-thiocyanatoethylnaphthalene is displayed in its thermal isomerisation, and in its replacement by nucleophilic reagents.

PART IV [1] included observations on the reactivity of the naphthalene nucleus towards thiocyanogen chloride. Unsubstituted naphthalene was moderately reactive, whereas unsubstituted benzene was inert; and 1- and 2-methylnaphthalene were almost as reactive as 1,3,5-trimethylbenzene. Subsequent examination of the products from 1-methylnaphthalene showed that the methyl group was as readily thiocyanated as the nucleus. The contributions of nuclear and side-chain substitution have therefore been ascertained for this hydrocarbon under varying conditions (Table 1), and briefer investigations have been made with 2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-t-butyl-naphthalene (Table 2).

Comparison of the 2-alkyl rather than the 1-alkyl homologues was convenient because the former series is the more readily accessible from Friedel–Crafts reactions. 2-Ethylnaphthalene is best prepared [2,3] by reduction of the crystalline 2-acetyl derivative, which

[1] Part IV, preceding paper.
[2] Lévy, *Ann. Chim.* (*France*), 1938, **9**, 5.
[3] For preparations of alkylnaphthalenes, see Hickinbottom and Porter, *J. Inst. Petroleum*, 1949, **35**, 621; Luther and Wächter, *Chem. Ber.*, 1949, **82**, 161; Anderson, Smith, and Rallings, *J.*, 1953, 443; Wibaut, van Nes, and Stofberg, *Rec. Trav. chim.*, 1954, **73**, 501; Bailey, Smith, and Staveley, *J.*, 1956, 2731.

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TABLE 1. *Reactions between* 1-*methylnaphthalene* (1 *mol.*) *and thiocyanogen chloride* (2 *mol.*) *in solution* (500 *ml.*), *yielding* 1-*methyl*-4-*thiocyanatonaphthalene* (I) *or* 1-*thiocyanatomethylnaphthalene* (II).

	Cl·SCN concn. (M)	Solvent	Illumination, etc.	Temp.	Total time (hr.)	Total Cl·SCN consumed [a] (mol.)	Yield of nuclear isomer [b] (I) (mol.)	Yield of side-chain isomer [b] (II) (mol.)
(i)	0·161	AcOH	Darkness	20°	25	1·12	0·92	Nil
(ii)	0·132	,,	,,	,,	,,	1·10	0·88	Nil
(iii)	0·105	CCl_4	,,	,,	124	0·66	Nil	Nil
(iv)	0·104	,,	Darkness; 0·2 g. Bz_2O_2	78	1	2·00	Nil	0·65
(v)	0·069	AcOH	Lab. daylight [c]	20	25	0·98	0·68	0·02
(vi)	0·136	,,	,,	,,	,,	1·16	0·71	0·08
(vii)	0·112	,,	,,	,,	,,	1·16	0·53	0·11
(viii)	0·093	,,	,,	,,	,,	1·16	0·44	0·32
(ix)	0·154	,,	,,	40	10	1·32	0·81	0·03
(x)	0·122	,,	W-filament lamp (500 w)	26	3	1·00	0·64	0·08
(xi)	0·131	,,	do., plus daylight	22	,,	0·99	0·53	0·18
(xii)	0·100	,,	Hg-vapour lamp	33	0·5	1·08	0·20	0·62
(xiii)	0·080	,,	,,	43	1·5	1·40	0·18	0·57
(xiv)	0·082	,,	,,	43	3	1·50	0·21	0·55
(xv)	0·126	,,	,,	39	,,	1·46	0·21	0·52
(xvi)	0·250	,,	,,	43	,,	1·64	0·46	0·46
(xvii)	0·092 $(SCN)_2$	,,	,,	49	7	0·58 $(SCN)_2$	Nil	0·40
(xviii)	0·107	CCl_4	,,	47	1·5	1·24	Nil	0·78
(xix)	0·090 $(SCN)_2$	,,	,,	47	3	0·92 $(SCN)_2$	Nil	0·50

[a] From iodometric titration. [b] Determined from infrared absorption curves and checked (expts. v—ix) by chromatographic separation (see Experimental section). [c] Expts. (v)—(ix) were performed in laboratory daylight during the months October—March.

TABLE 2. *Reaction between* 2-*alkylnaphthalenes and thiocyanogen chloride in solution* (500 *ml.*), *yielding* 2-*alkyl*-1-*thiocyanatonaphthalenes* (III) *or* 2-α-*thiocyanatoalkylnaphthalenes* (IV).

	2-Alkyl subst.	Cl·SCN Concn. (M)	Solvent	Cl·SCN/ $C_{10}H_7Alk.$ (mol. ratio)	Illumination, etc.	Temp.	Total time (hr.)
(i)	Me	0·157	AcOH	1 : 0·5	Darkness	20°	34
(ii)	,,	0·124	,,	,,	Daylight	,,	30
(iii)	,,	0·090	CCl_4	1 : 5	Hg lamp [c]	37	5
(iv)	Et	0·187	AcOH	1 : 0·5	Darkness	20	70
(v)	,,	0·090	CCl_4	1 : 5	Hg lamp [c]	37	2·5
(vi)	,,	0·112	,,	1 : 0·5	Darkness; 0·07 g. Bz_2O_2	78	4
(vii)	Pr^i	0·095	AcOH	,,	Darkness	20	250
(viii)	,,	0·216	$CHCl_3$ (125 ml.)	1 : 2	Daylight; 1·5 g. $AlCl_3$	,,	1·5
(ix)	,,	0·086	CCl_4	1 : 0·55	Hg lamp [c]	37	2·3
(x)	Bu^t	0·120	AcOH	1 : 0·5	Darkness	20	240
(xi)	,,	0·105	CCl_4	1 : 2	Hg lamp [c]	30	2

	Cl·SCN consumed [a] (mol.)	Yield of nuclear isomer [b] (III) (%)	Yield of side-chain isomer [b] (IV) (%)		Cl·SCN consumed [a] (mol.)	Yield of nuclear isomer [b] (III) (%)	Yield of side-chain isomer [b] (IV) (%)
(i)	0·57	81	Nil	(vii)	0·72	20	Nil
(ii)	0·54	29	19	(viii)		20	Nil
(iii)	0·70	Nil	25	(ix)	0·75	Nil	10 [d]
(iv)	0·65	60	Nil	(x)	0·79	30	Nil
(v)	0·86	Nil	33	(xi)	0·05	Nil	Nil
(vi)	0·52	Nil	30				

[a] From iodometric titration. [b] Yields are calculated with reference to whichever reagent, Cl·SCN or alkylnaphthalene, was used in the lower proportion. [c] Irradiation by a 250 w "Mazda" ME/D mercury-vapour lamp (ref. 1). [d] This product was the isothiocyanate.

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results from acetylation of naphthalene in nitrobenzene solution.[2,4] For 2-isopropylnaphthalene, an alkylation procedure used in a synthesis by Haworth and his co-workers [5] was followed; to check the structure, they also carried out a synthesis with a sample of 2-isopropylnaphthalene prepared from 2-acetylnaphthalene, and likewise (see below), when requiring an alternative route to the α-thiocyanation product of 2-isopropylnaphthalene, we based the second synthesis on the same ketone. 2-t-Butylnaphthalene has been frequently prepared by alkylation; distinction between the 2- and the 1-isomer has been made by Peters and his co-workers.[6] Since we have never isolated isomeric thiocyanation products other than those due to competitive reactivity of the nucleus and side chain, our hydrocarbon samples were not significantly heterogeneous.

The two products obtainable from 1-methylnaphthalene and thiocyanogen chloride (Table 1) were 1-methyl-4-thiocyanatonaphthalene and 1-thiocyanatomethylnaphthalene. The structure of the nuclear thiocyanate was proved, as in earlier cases,[1] by an alternative preparation from diazotised 4-methyl-1-naphthylamine. The other product was alternatively obtained by the reaction of 1-chloromethylnaphthalene with thiocyanate ion, as had been described in a patent.[7] The two isomers were quantitatively separated by chromatography with silica gel, on which the nuclear thiocyanate was the less strongly absorbed. Both showed the characteristic sharp absorption peak, due to thiocyanate, at 2160 cm.$^{-1}$ in their infrared spectra.[1] The thiocyanato-structure was also demonstrated chemically, in these and other cases, by conversion of the product into a thiol with lithium aluminium hydride,[1] or into a disulphide by alkaline fission of the S–CN bond.[8] The products from 1-methylnaphthalene were differentiated by the reactivity towards silver nitrate of the isomer containing the thiocyanatomethyl group and by the very different infrared absorption peaks which they showed in the 700—800 cm.$^{-1}$ region. The latter property was used for analysis of mixed thiocyanation products, and the results agreed closely with those obtained by the more tedious chromatographic separation of the isomers.

For the range of conditions summarised in Table 1, illumination and the nature of the solvent were the dominant factors controlling the product. In darkness, thiocyanation occurred wholly in the nucleus, and in high yield, if the solvent was acetic acid, but there was no reaction if the solvent was carbon tetrachloride. In daylight, and with acetic acid as solvent, nuclear thiocyanation was still the main result, but it was always accompanied by a minor and non-reproducible degree of substitution in the methyl group. Illumination by a tungsten-filament lamp had a similar effect to daylight. When a powerful mercury-vapour lamp [1] was used, reaction was substantially greater in the methyl group than in the nucleus, if the solvent was acetic acid, and it occurred entirely in the methyl group if the solvent was carbon tetrachloride. These facts suggest, as in the case of *m*-xylene already discussed,[1] that a homolytic, light-induced reaction in the methyl group is competing with a solvent-assisted heterolytic reaction in the nucleus. The beneficial effect of a polar solvent on nuclear substitutions by thiocyanogen chloride had been noted previously.[9] The homolytic character of the side-chain reaction is supported by the observation (expt. iv) that it could be induced in carbon tetrachloride in darkness if a peroxide was present to initiate radical chains. A further point of interest (expts. xvii, xix) is that thiocyanogen was successfully used in place of thiocyanogen chloride to achieve the homolytic reaction, though, in accordance with its known inferiority for heterolytic reactions,[1,9] thiocyanogen failed to attack the nucleus of 1-methylnaphthalene, even in

[4] Baddeley, *J.*, 1949, S 99; higher homologues were similarly prepared by Buu-Hoï and Cagniant, *Bull. Soc. chim. France*, 1945, **12**, 307.

[5] Haworth, Letsky, and Mavin, *J.*, 1932, 1784.

[6] (*a*) Bromby, Peters, and Rowe, *J.*, 1943, 144; (*b*) Contractor, Peters, and Rowe, *J.*, 1949, 1993; (*c*) Illingworth and Peters, *J.*, 1951, 1602.

[7] Jones and American Chemical Paint Co., U.S.P. 2,394,915/1946.

[8] Bacon, "Thiocyanates, Thiocyanogen, and Related Compounds," in "Organic Sulphur Compounds," Pergamon Press, London, Vol. I, in the press.

[9] Bacon and Guy *J.*, 1960, 318.

acetic acid solution. Homolytic reactions of thiocyanogen have been the subject of later investigations.[10,11]

2-Methylnaphthalene showed the same features as the 1-isomer in its reactions with thiocyanogen chloride (Table 2). The two products, 2-methyl-1-thiocyanatonaphthalene and 2-thiocyanatomethylnaphthalene, were characterised as already described for the 1-methylnaphthalene derivatives, and their identity was checked by the preparation of samples from 2-methyl-1-naphthylamine and 2-bromomethylnaphthalene respectively.

For substitutions of benzene derivatives, similarities between the behaviour of thiocyanogen chloride and that of the halogens have been noted.[1,9] Such similarities are likewise evident when the literature concerning halogenation of 1- and 2-methylnaphthalene is studied; information about their higher homologues is negligible. If nuclear chlorination or bromination is desired, unaccompanied by substitution in the methyl group, light should be excluded and high temperatures avoided.[12] Photobromination of 2-methylnaphthalene in carbon tetrachloride, with light of varying wavelength, was reported in one publication to cause only a small proportion of substitution in the methyl group,[13] but elsewhere 40—80% yields of the bromomethyl compound have been claimed.[14,15] *N*-Bromosuccinimide normally brominates the methyl group of 2-methylnaphthalene, but substitution can be transferred to the nucleus by the presence of traces of impurities.[14] It is well known that the efficacy of this reagent for aromatic side-chain substitution in general is greatly influenced by the solvent,[16] and recent observations in the benzene series show that, when the solvent is appropriately chosen, nuclear substitution may occur instead.[17] Results of the chlorination of 1-methylnaphthalene by *N*,2,4,6-tetrachloroacetanilide [18] show a marked similarity to those reported here for thiocyanogen chloride; in acetic acid, in the dark, 90% of the substitution was nuclear, but in carbon tetrachloride, with benzoyl peroxide present, it occurred entirely in the methyl group. All these reactions seem to involve competition between ionic and radical substitution processes, affecting the naphthalene nucleus and side chain respectively. However, this simple view might not survive a more detailed examination, for Mayo and Hardy's extensive study of the bromination of naphthalene [19] revealed unexpected complexity of mechanism.

Thiocyanation experiments with the higher homologues (Table 2) were confined to the use of acetic acid solutions in darkness for nuclear reaction, and of irradiated carbon tetrachloride solutions for reaction in the side chain. Under the former conditions, 2-ethylnaphthalene gave 2-ethyl-1-thiocyanatonaphthalene, and under the latter conditions, or with initiation by benzoyl peroxide instead of light, it gave 2-1′-thiocyanatoethylnaphthalene. The structures of these thiocyanates were proved by the presence of a sharp peak at 2150 cm.$^{-1}$ in their infrared absorption spectra; by reduction and other chemical reactions (see below); and by their synthesis from 2-ethyl-1-naphthylamine and 2-1′-bromoethylnaphthalene respectively. The 1-amine was obtained from 2-ethylnaphthalene by nitration and reduction, as described by Lévy,[2] who proved the intermediate to be 2-ethyl-1-nitronaphthalene by an unambiguous synthesis of 2-ethyl-1-naphthol, which he also prepared from the amine.

The nuclear thiocyanate from 2-isopropylnaphthalene, obtained in acetic acid in darkness, was considered, by analogy with the lower homologues, to be 2-isopropyl-1-thiocyanatonaphthalene. The yield was not improved when aluminium chloride was tried as

[10] Bacon, Guy, Irwin, and Robinson, *Proc. Chem. Soc.*, 1959, 304.
[11] Bacon and Irwin, following paper.
[12] *E.g.*, Mayer and Sieglitz, *Ber.*, 1922, **55**, 1835; Robinson and Thompson, *J.*, 1932, 2015.
[13] King and Sampey, *J. Org. Chem.*, 1949, **14**, 470.
[14] Chapman and Williams, *J.*, 1952, 5044.
[15] Keene and Schofield, *J.*, 1957, 3181.
[16] Horner and Winkelmann, *Angew. Chem.*, 1959, **71**, 349.
[17] Ross, Finkelstein, and Petersen, *J. Amer. Chem. Soc.*, 1958, **80**, 4327.
[18] Ayad, Beard, Garwood, and Hickinbottom, *J.*, 1957, 2981.
[19] Mayo and Hardy, *J. Amer. Chem. Soc.*, 1952, **74**, 911.

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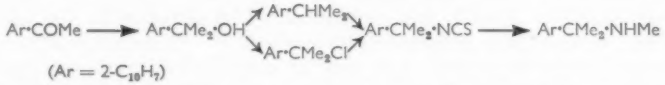
catalyst.[20] The product of side-chain thiocyanation, obtained in irradiated carbon tetrachloride solution, was 2-isothiocyanato-2-2′-naphthylpropane. This was expected, since thiocyanation of isopropylbenzene had given an unstable thiocyanate, readily isomerising to the isothiocyanate during isolation,[1] and our general experience has been that the ease of an isomerisation, $>$CAr·SCN ⟶ $>$CAr·NCS, is increased when Ar is a naphthyl instead of a phenyl group.[8] The isothiocyanate structure was proved by the absence of the –SCN peak, and the presence of the broad –NCS peak at 2080 cm.$^{-1}$ in the infrared absorption spectrum; by the formation of an addition product, 2-$C_{10}H_7$·CMe_2·NH·CS·NR (NR = morpholino); and by reduction to 2-methylamino-2-2′-naphthylpropane with lithium aluminium hydride, under conditions described for phenyl isothiocyanate.[21] The reduction and an alternative synthesis of the isothiocyanate are shown in the annexed scheme.



2-2′-Naphthylpropan-2-ol was used as an intermediate both for the corresponding chloride and for an alternative preparation of 2-isopropylnaphthalene, which it gave on reductive dehydroxylation with Raney nickel.[22] The chloride was very reactive, and rapidly gave the isothiocyanate exclusively when treated with ammonium thiocyanate in acetone solution at room temperature. Regarded generally, replacements of halides can give a thiocyanate, an isothiocyanate, or a mixture of the two,[8] and the observed result again shows the influence of a constituent naphthyl group in favouring the iso-form.

The failure of 2-t-butylnaphthalene to undergo thiocyanation in irradiated carbon tetrachloride solution was expected, because of the absence of an α-hydrogen atom. The nuclear thiocyanation product, obtained in acetic acid solution, was considered, again by analogy, to be 2-t-butyl-1-thiocyanatonaphthalene. The 1-position in 2-t-butylnaphthalene, as in ethylnaphthalene,[2] is known to be the point of entry for a nitro-group,[6b] though sulphonation occurs in the other ring in both of these hydrocarbons.[2,6b,23] Comparison of the results in Table 2 suggests a decline in nuclear activity as the number of methyl groups attached to the α-carbon atom of the 2-alkyl group is increased; this could be due to steric hindrance at the 1-position.

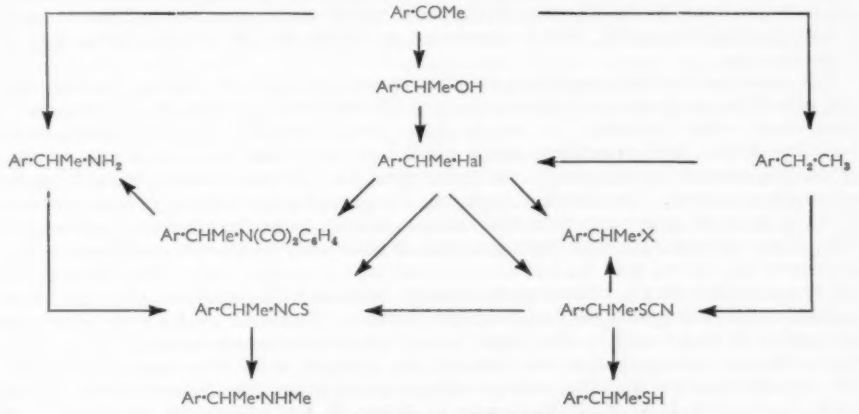
Finally, in the annexed scheme, we summarise a number of reactions involving thiocyanato- and other side-chain derivatives of 2-ethylnaphthalene.

The 1′-thiocyanate, obtained by homolytic thiocyanation, was also prepared, in high yield, by reaction of the 1′-bromo- or 1′-chloro-compound with ammonium thiocyanate in boiling acetone. When boiling ethanol was used, solvolysis intervened, and the resulting 1′-ethoxide was accompanied by both the 1′-thiocyanate and the 1′-isothiocyanate, separable by chromatography with silica gel, on which the isothiocyanate was the less strongly absorbed. As in some other cases in which a mixture of isomers results from reactions of halides with thiocyanate ion,[8] this result does not seem to be due to the thermal instability of the thiocyanato-form.

2-1′-Isothiocyanatoethylnaphthalene was also prepared through the dithiocarbamate,[24] obtained from 2-1′-aminoethylnaphthalene. The isothiocyanate and the thiocyanate were distinguished by infrared spectral characteristics and by reduction with lithium aluminium hydride, which gave the 1′-methylamino-derivative and the 1′-thiol, respectively. The thiocyanate was isomerised into the isothiocyanate at a distillation temperature of 140—150°; heating for 1 hr. in closed tubes at 120—150° resulted in a 70—80% yield of the isothiocyanate, the concentration of which was determined from the intensity of the very

[20] Cf. Söderbäck, *Acta Chem. Scand.*, 1954, **8**, 1851.
[21] Ried and Müller, *Chem. Ber.*, 1952, **85**, 470.
[22] Cf. Zderic, Bonner, and Greenlee, *J. Amer. Chem. Soc.*, 1957, **79**, 1696.
[23] Buu-Hoï, Le Behan, and Leroux, *J. Org. Chem.*, 1953, **18**, 582.
[24] Cf. *Org. Synth.*, Coll. Vol. III, p. 599.

strong band at 2095 cm.$^{-1}$ in the infrared absorption spectrum. Thermal instability was considerably greater in 2-1′-isothiocyanatoethylnaphthalene than in 1′-thiocyanatoethylbenzene, an observation which again shows the extra mobility conferred by a naphthyl



(Ar = 2-$C_{10}H_7$; Hal = Cl or Br; X = OEt or thiouronium picrate)

substituent in comparison with a phenyl substituent. The thermally promoted isomerisation, R·SCN ⟶ R·NCS, is well known, but other manifestations of mobility in thiocyanates, such as replacements, R·SCN ⟶ RX, or elimination of HSCN, *i.e.*, reactions akin to those of halides, are not well known. Experiments incidentally carried out with 2-1′-thiocyanatoethylnaphthalene involved two such replacements, namely, conversion by thiourea into a thiouronium salt, and by boiling ethanol into the 1′-ethoxide. This type of reaction will be discussed in a later paper.

Experimental

The procedure for thiocyanation in acetic acid solution was described in Parts III [9] and IV; [1] the procedure for photo-initiated thiocyanation was described in Part IV. Consumption of thiocyanogen chloride was determined, as previously described,[9,25] by iodometric titration of aliquot parts of the reaction mixtures. Products were isolated as described in the earlier papers.

Estimation of Mixed Isomeric Thiocyanation Products.—(*a*) When a reaction yielded two isomeric thiocyanates (Table 1; Table 2, expt. ii), these were separated by chromatography of the crude product on a column of silica gel with benzene–light petroleum, the proportion of benzene being gradually increased; further details are given for individual cases below. Fractions of volume ~70 ml. were collected.

(*b*) A method of analysis was developed for mixtures of 1-methyl-4-thiocyanatonaphthalene and 1-thiocyanatomethylnaphthalene (Table 1), based on differences in infrared absorption characteristics of these compounds. The former gives a strong, sharp peak at 752 cm.$^{-1}$ and the latter gives a strong, sharp peak at 722 cm.$^{-1}$. For each of these absorption peaks, optical density showed a strictly linear relation with concentration when examined over the range 1—160 mg. of thiocyanate per 5 ml. of carbon disulphide solution. The two peaks were clearly differentiated in solutions of the mixed isomers, and the concentrations of the two components, calculated from optical densities, were in close agreement (±1%) with the expected values in mixtures of known composition.

The presence of unchanged 1-methylnaphthalene interfered with this estimation and the hydrocarbon was accordingly eluted from the crude reaction product by adding a solution of the product in 3 : 1 benzene–light petroleum to a column of silica gel, and eluting the hydrocarbon with the same solvent mixture. The mixed hydrocarbon-free fractions were dissolved

[25] Angus and Bacon, *J.*, 1958, 774; Bacon and Irwin, *J.*, 1958, 778.

in acetone, and an aliquot part of the solution, containing ~0·10 g. of product, was transferred to a graduated flask and evaporated. The volume was made up to 5 ml. in carbon disulphide for infrared spectroscopy, which was carried out in a Perkin–Elmer Model 21 spectrophotometer. The correspondence found between the chromatographic and the spectroscopic method of analysis is illustrated by the following yield figures, which refer to expt. (ix) in Table 1: isomer (I), 81% by chromatography, 82% by spectroscopy; isomer (II), 3% by chromatography 4% by spectroscopy.

Thiocyanation of 1-*Methylnaphthalene.*—The experiments (Table 1) were carried out with a pure, redistilled sample of the hydrocarbon, b. p. 121°/19 mm., n_D^{25} 1·6148. It proved to be homogeneous when subjected to vapour-phase chromatography (Argon Chromatograph, W. G. Pye & Co.), under conditions which would have led to the detection of any 2-methylnaphthalene present in the sample. A typical procedure for the isolation of thiocyanation products is as follows. The reaction (expt. vii) was carried out on 3·89 g. of hydrocarbon in 500 ml. of an acetic acid solution of thiocyanogen chloride under the conditions given in the Table. Lead chloride,[9] left from the preparation of thiocyanogen chloride, was filtered off, and the solution was diluted with 3·5 l. of ice-water and kept overnight at 0°. Filtration yielded a light brown solid (4·53 g.), which was dissolved in benzene–light petroleum (1 : 1) for chromatography and eluted with the same solvent mixture. Fractions 2—4 yielded unchanged hydrocarbon (0·44 g.), and 7—21 yielded 1-*methyl*-4-*thiocyanatonaphthalene* (2·89 g., 53%), which, after one recrystallisation from ethanol, was obtained in colourless needles, m. p. 70—70·5°, not depressed on admixture with a sample prepared as described below (Found: C, 72·2; H, 4·4; N, 6·95; S, 15·8. $C_{12}H_9NS$ requires C, 72·35; H, 4·55; N, 7·0; S, 16·1%), $\lambda_{max.}$ 225 (log ε 4·74) and 292 mμ (log ε 3·94).

Elution was continued with benzene and yielded 1-thiocyanatomethylnaphthalene (0·61 g., 11%) in fractions 25—33. One recrystallisation from ethanol gave this isomer as prisms, m. p. 88—90° (lit.,[7] 91—91·5°), not depressed on admixture with a sample prepared as described below (Found: C, 71·95; H, 4·55; N, 6·85; S, 16·25%), $\lambda_{max.}$ 224 (log ε 4·76) and 284 mμ (log ε 3·92). It gave a precipitate with ethanolic silver nitrate and was converted, as described below, into di-1-naphthylmethyl disulphide, m. p. and mixed m. p. 108—109°.

For an alternative synthesis of 1-methyl-4-thiocyanatonaphthalene, nitration [26,27] of 1-methylnaphthalene (0·14 mole) gave a crude product (9 g.) which was purified by chromatography on alumina with 1 : 1 benzene–light petroleum, and by recrystallisation from ethanol, 1-methyl-4-nitronaphthalene being obtained in yellow needles (4·45 g., 17%), m. p. 64—67° (lit.,[26] 71—72°). This was reduced, as described for the 2-methyl-1-nitro-isomer,[28] with stannous chloride, and the resulting tin complex was decomposed, in solution, by aqueous potassium hydroxide, and 4-methyl-1-naphthylamine was obtained, on ether-extraction, as a brown solid (95%), m. p. 45—49° (lit.,[26] 51—52°). Its ethereal solution was treated with sulphuric acid to give the sulphate (80%), and the latter (0·02 mole) was diazotised and treated with ferric thiocyanate as previously described [1] for 2,4-dimethylaniline. The crude product (71%), obtained by ether-extraction, was purified by chromatography on silica gel with benzene–light petroleum (3 : 2, changing to 4 : 1), and by recrystallisation of fractions 9—17 (2·15 g., 57%) from ethanol; 1-methyl-4-thiocyanatonaphthalene was thus obtained in colourless needles, m. p. 70—70·5°.

For an alternative preparation of 1-thiocyanatomethylnaphthalene, an ethanolic solution of 1-chloromethylnaphthalene [29] and ammonium thiocyanate (1·1 mol.) was refluxed for 1·5 hr. Dilution with water precipitated the product in quantitative yield, and recrystallisation from ethanol gave prisms, m. p. 88—90°. For conversion into the disulphide, the thiocyanate (0·005 mole) in ethanol (40 ml.) was treated with sodium hydroxide (0·01 mole) in water (10 ml.) and ethanol (20 ml.), and the mixture was left overnight. The pale yellow precipitate (85%) was purified by chromatography with benzene–light petroleum (1 : 1) on silica gel; some yellow oil remained on the column and di-1-naphthylmethyl disulphide was obtained in colourless needles, m. p. 108—109° (lit.,[30] 108·5—109°) after recrystallisation from acetone (Found: C, 76·5; H, 5·25; S, 18·15. Calc. for $C_{22}H_{18}S_2$: C, 76·3; H, 5·25; S, 18·5%).

[26] Lesser, *Annalen*, 1913, **402**, 1.
[27] Thompson, *J.*, 1932, 2310.
[28] Fierz-David and Mannhart, *Helv. Chim. Acta*, 1937, **20**, 1024.
[29] *Org. Synth.*, Coll. Vol. III, p. 195.
[30] Windus and Turley, *J. Amer. Leather Chemists' Assoc.*, 1938, **33**, 246.

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Thiocyanation of 2-Methylnaphthalene.—(*a*) Under the conditions given for expt. (i) in Table 2, 5·56 g. of 2-methylnaphthalene yielded 7·31 g. of pale yellow solid, m. p. 85—90°, when the reaction mixture was diluted with ice-water. A portion of this (3·40 g.) was chromatographed with benzene–light petroleum (7 : 3), yielding, in fractions 2—3, unchanged hydrocarbon (0·27 g.), and, in fractions 5—12, *2-methyl-1-thiocyanatonaphthalene* (2·95 g., corresponding to 81% yield), m. p. 99—102°; when recrystallised from ethanol it gave long, colourless needles, m. p. 101—102°, not depressed on admixture with a sample prepared as described below (Found: C, 72·4; H, 4·5; N, 6·65; S, 15·9. $C_{12}H_9NS$ requires C, 72·35; H, 4·55; N, 7·0; S, 16·1%), $\lambda_{max.}$ 224 (log ε 4·75) and 288 mμ (log ε 3·79). No other product was obtained from the column.

For an alternative synthesis of this compound, 2-methylnaphthalene was converted [28] into 2-methyl-1-nitronaphthalene (24%), and thence into 2-methyl-1-naphthylamine (82%), which was diazotised and treated with ferric thiocyanate as described [1] for 2,4-dimethylaniline. The crude product was chromatographed on silica gel with 3 : 2 benzene–light petroleum. The fractions containing 2-methyl-1-thiocyanatonaphthalene (56%) gave needles, m. p. 101—102°, when recrystallised from ethanol.

(*b*) Under the conditions given for expt. (ii) in Table 2, 4·39 g. of the hydrocarbon yielded 5·24 g. of crude product, 3·75 g. of which were chromatographed. Unchanged hydrocarbons (fractions 3—7; 1·04 g.) were eluted by 1 : 3 benzene–light petroleum; 2-methyl-1-thiocyanatonaphthalene (fractions 23—30; 1·29 g., corresponding to 29% yield) was eluted by 3 : 2 benzene–light petroleum; and *2-thiocyanatomethylnaphthalene* (fractions 32—37; 0·83 g., 19% yield), m. p. 93—98°, was eluted by benzene. The 2-thiocyanatomethylnaphthalene was obtained in small, colourless needles, m. p. 101—101·5°, when recrystallised from carbon tetrachloride (Found: C, 72·2; H, 4·55; N, 6·8; S, 15·9. $C_{12}H_9NS$ requires C, 72·55; H, 4·55; N, 7·0; S, 16·1%), $\lambda_{max.}$ 225 (log ε 4·78) and 274 mμ (log ε 3·72). This compound showed no depression of m. p. on admixture with the sample prepared as described below, but showed a large depression in m. p. with the nuclear-substituted isomer, of similar m. p., described above. M. p. 101° was also shown by the sample of 2-thiocyanatomethylnaphthalene obtained by irradiation under the conditions given for expt. (iii) in Table 2.

For an alternative synthesis of 2-thiocyanatomethylnaphthalene, *N*-bromosuccinimide was used [31] to convert 2-methylnaphthalene into 2-bromomethylnaphthalene (65%), m. p. 52—55° (lit.,[31] 56°), which was treated with a slight excess of ammonium thiocyanate for 3 hr. in boiling ethanol. Dilution with water and recrystallisation of the precipitated product from carbon tetrachloride gave 2-thiocyanatomethylnaphthalene, m. p. 101—101·5°.

Ethylnaphthalene.—Reaction [2,4] between naphthalene (2 moles), acetyl chloride (2 moles), and anhydrous aluminium chloride (2 moles) in nitrobenzene (1 l.) gave 2-acetylnaphthalene, b. p. 128—130°/0·7 mm., which crystallised from light petroleum in prisms (47%), m. p. 52° (lit.,[2,4] 53·5°). The ketone was reduced by Huang-Minlon's method: [32] 2-acetylnaphthalene (0·8 mole), potassium hydroxide (2·8 moles), and 100% hydrazine hydrate (2·4 moles) in diethylene glycol (1100 ml.) were heated under reflux for 1·5 hr.; excess of hydrazine and water were then distilled off until the temperature of the liquid reached 200° (1·5 hr.) and refluxing was continued for 4 hr. The cooled solution was added to ice and water (4 l.), neutralised with sulphuric acid, and extracted with ether, 2-ethylnaphthalene being obtained (78%) with b. p. 118°/12 mm., n_D^{25} 1·5987.

Thiocyanation of 2-Ethylnaphthalene.—(*a*) Under the conditions given for expt. (iv) in Table 2, 7·28 g. of 2-ethylnaphthalene gave 9·19 g. of a crude brown oil which was chromatographed on silica gel with benzene–light petroleum (1 : 9, changing to 1 : 1). This yielded *2-ethyl-1-thiocyanatonaphthalene* (6·00 g., 60%), which crystallised from methanol in colourless, vesicant prisms, m. p. 54·5°, not depressed on admixture with a sample prepared as described below (Found: C, 73·15; H, 5·0; N, 6·2; S, 15·05. $C_{13}H_{11}NS$ requires C, 73·2; H, 5·2; N, 6·6; S, 15·0%). No other crystalline product was obtained from the chromatogram. By the procedure previously described,[1] the thiocyanate was characterised by reduction with lithium aluminium hydride and conversion of the resulting liquid thiol into *2-ethyl-1-naphthyl 2,4-dinitrophenyl sulphide*, which crystallised from ethanol in yellow needles, m. p. 117° (Found: C, 60·9; H, 3·9; N, 7·9; S, 8·7. $C_{18}H_{14}N_2O_4S$ requires C, 61·0; H, 4·0; N, 7·9; S, 9·0%).

For an alternative synthesis of 2-ethyl-1-thiocyanatonaphthalene, the hydrocarbon (0·2 mole)

[31] Buu-Hoï, *Annalen*, 1944, **556**, 1.
[32] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

was converted [2] into 2-ethyl-1-nitronaphthalene (25%), m. p. 50·5° (lit.,[2] 49·5—50°), and thence into 2-ethyl-1-naphthylamine [2] (44%), which was diazotised and treated with ferric thiocyanate, as described [1] for 2,4-dimethylaniline. Decomposition was completed on the steam-bath, and the product was taken up in benzene, purified on a column of alumina, and recrystallised from methanol, which gave prisms (57%), m. p. 54°.

(*b*) After thiocyanation under the conditions given for expt. (v) in Table 2, solvent was removed and excess of hydrocarbon was distilled off at 165°/0·03 mm. The brown residue was chromatographed on silica gel with benzene–light petroleum; a 1 : 1 solvent mixture eluted 2-1′-*thiocyanatoethylnaphthalene* (33%), which recrystallised from light petroleum as prisms, m. p. 52·5°, not depressed on admixture with a sample prepared as described below (Found: C, 73·4; H, 5·1; N, 6·7; S, 15·3. $C_{13}H_{11}NS$ requires C, 73·2; H, 5·2; N, 6·6; S, 15·0%). The thiocyanation (expt. vi) involving benzoyl peroxide was conducted at the b. p. because only 5% consumption of reagent was observed in 4 hr. at 50°. When the experiment was repeated at the b. p. in the absence of peroxide most of the ethylnaphthalene was recovered unchanged and no thiocyanation product was observed.

The following paragraphs describe an alternative route to 2-1′-thiocyanatoethylnaphthalene, some reactions of the compound, and the preparation of other derivatives of ethylnaphthalene.

2-1′-*Hydroxyethylnaphthalene*.—2-Acetylnaphthalene (see above) (0·15 mole) in ether (50 ml.) was added during 20 min. to a slurry of lithium aluminium hydride (0·044 mole) in ether (60 ml.), and the mixture was refluxed for 1 hr. The product was decomposed by water and then by 10% sulphuric acid, and the ether solution was washed with aqueous sodium hydrogen carbonate and evaporated; 2-1′-hydroxyethylnaphthalene was obtained (24·1 g., 95%) as prisms, m. p. 72—74° (lit.,[33] 72°), by recrystallisation from light petroleum (Found: C, 83·7; H, 6·6. Calc. for $C_{12}H_{12}O$: C, 83·7; H, 7·0%).

2-1′-*Bromoethylnaphthalene*.—A solution of 2-1′-hydroxyethylnaphthalene (0·125 mole) in benzene (200 ml.) was treated with dry hydrogen bromide until an aqueous layer had separated (30 min.). The organic layer was washed with dilute aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure. The residue of 2-1′-*bromoethylnaphthalene* recrystallised from light petroleum as prisms (23·5 g., 80%), m. p. 63—64° (Found: C, 61·1; H, 4·9; Br, 33·85. $C_{12}H_{11}Br$ requires C, 61·3; H, 4·7; Br, 34·0%). Alternatively, a solution of 2-ethylnaphthalene (0·1 mole), *N*-bromosuccinimide (0·1 mole), and benzoyl peroxide (0·1 g.) in dry carbon tetrachloride (80 ml.) was refluxed for 4·5 hr., and the warm solution was filtered and evaporated, giving 2-1′-bromoethylnaphthalene (91%), m. p. 63°, on recrystallisation. The bromide was treated with an equal weight of thiourea for 20 min. in boiling ethanol; after addition of picric acid and cooling, S-(1-2′-*naphthylethyl*)*thiouronium picrate* separated, and recrystallised from aqueous ethanol as yellow needles, m. p. 202° (Found: C, 50·0; H, 4·0; N, 15·3; S, 6·8. $C_{19}H_{17}N_5O_7S$ requires C, 49·7; H, 3·7; N, 15·25; S, 7·0%).

2-1′-*Chloroethylnaphthalene*.—Treatment of 2-1′-hydroxyethylnaphthalene (0·15 mole) with dry hydrogen chloride, as described for the bromide, gave 2-1′-*chloroethylnaphthalene* (24·5 g., 86%), crystallising from light petroleum in prisms, m. p. 67° (Found: C, 75·6; H, 5·7. $C_{12}H_{11}Cl$ requires C, 75·6; H, 5·8%). It likewise gave the thiouronium picrate, m. p. 202°.

2-1′-*Thiocyanatoethylnaphthalene*.—Ammonium thiocyanate (0·225 mole) was heated with 2-1′-bromoethylnaphthalene (0·075 mole) in acetone (125 ml.) for 1 hr. under reflux. After addition of the mixture to water, extraction with ether gave 2-1′-thiocyanatoethylnaphthalene (12 g., 75%), m. p. 52·5°, after recrystallisation from light petroleum. 2-1′-Chloroethylnaphthalene and ammonium thiocyanate (3 mol.) likewise gave the 2-1′-thiocyanate (90%), after 3·5 hr. in refluxing acetone. The thiocyanate showed a strong, sharp peak at 2150 $cm.^{-1}$ in the infrared absorption spectrum (5% solution in carbon tetrachloride). When treated with thiourea, under conditions used for the bromide (see above), it was converted into *S*-(1-2′-naphthylethyl)thiouronium picrate, m. p. and mixed m. p. 202°. When reduced with lithium aluminium hydride (1·2 mol.), the thiocyanate formed 1-2′-*naphthylethane*-1-*thiol* (96%), b. p. 122°/0·7 mm., prisms, m. p. 37—38° (Found: C, 76·35; H, 6·8; S, 16·7. $C_{12}H_{12}S$ requires C, 76·6; H, 6·4; S, 17·0%). The thiol could not be converted into a 2,4-dinitrophenyl sulphide; it formed unstable lead and mercury derivatives.

2-1′-*Aminoethylnaphthalene*.—Reaction was carried out between potassium phthalimide [34]

[33] Lund, *Ber.*, 1937, **70**, 1520.
[34] Hale and Britton, *J. Amer. Chem. Soc.*, 1919, **41**, 844.

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(0·12 mole) and 2-1′-bromoethylnaphthalene (0·11 mole), the solvent being dimethylformamide (90 ml.) as recommended [35] for this type of replacement. After brisk stirring at 70° for 2 hr., the mixture was cooled, and chloroform (135 ml.) was added, followed by water (450 ml.). The chloroform layer was washed with 0·2N-aqueous sodium hydroxide, dried, and evaporated. On trituration with light petroleum the residual gum yielded 2-1′-*phthalimidoethylnaphthalene*, which crystallised from ethanol in prisms (24·5 g., 74%), m. p. 100·5—102° (Found: C, 79·8; H, 5·25. $C_{20}H_{15}NO_2$ requires C, 79·8; H, 5·0%). This was decomposed by Ing and Manske's method,[36] giving the liquid 2-1′-aminoethylnaphthalene (80%), which formed the hydrochloride, m. p. 200—202° (from water) (lit.,[37] 198—199°). With benzoyl chloride and aqueous sodium hydroxide it gave 2-1′-*benzamidoethylnaphthalene*, m. p. 151·5° on recrystallisation from aqueous ethanol (Found: C, 83·1; H, 6·3; N, 4·95. $C_{19}H_{17}NO$ requires C, 82·9; H, 6·2; N, 5·1%). Alternatively, 2-1′-aminoethylnaphthalene was prepared from 2-acetylnaphthalene by the known [37] Leuckart method and isolated as the hydrochloride (52%), m. p. 200—202°.

2-1′-*Isothiocyanatoethylnaphthalene*.—(*a*) 2-1′-Aminoethylnaphthalene (6·80 g., 0·04 mole) and sodium hydroxide (0·04 mole) in water (7 ml.) were cooled to 10° and carbon disulphide (0·04 mole) was added with vigorous stirring during 30 min., accompanied by water (40 ml.), so that the resulting dithiocarbamate derivative was maintained as a slurry. This was stirred for 30 min. at 60° and was then decomposed with ethyl chloroformate (0·04 mole) at 35—40°, as described for methyl isothiocyanate.[24] 2-1′-*Isothiocyanatoethylnaphthalene* was extracted with ether and obtained as prisms (6·3 g., 73%) in one recrystallisation from light petroleum; two more recrystallisations removed yellow impurity and raised the m. p. to 49—50·5° (Found: C, 73·6; H, 5·5; N, 6·4; S, 15·3. $C_{13}H_{11}NS$ requires C, 73·2; H, 5·2; N, 6·6; S, 15·0%). The infrared absorption spectrum (5% solution in carbon tetrachloride) showed a very strong, broad band at 2090 cm.$^{-1}$. The isothiocyanate (1·00 g.) was treated with lithium aluminium hydride [21] (1·8 mol.) for 30 min. in boiling ether (25 ml.) and yielded 2-1′-*methylaminoethylnaphthalene* (0·76 g., 89%), b. p. 97°/0·5 mm. (Found: C, 83·5; H, 8·2; N, 7·5. $C_{13}H_{15}N$ requires C, 84·3; H, 8·1; N, 7·6%). It was characterised by conversion with 1-naphthyl isocyanate into N-*methyl*-N-1-2′-*naphthylethyl*-N′-1″-*naphthylurea*, which crystallised from ethanol in prisms, m. p. 154—155° (Found: C, 81·5; H, 6·2; N, 7·6. $C_{24}H_{22}N_2O$ requires C, 81·3; H, 6·2; N, 7·9%).

(*b*) A solution of 2-1′-chloroethylnaphthalene (0·12 mole) and ammonium thiocyanate (0·24 mole) in ethanol (200 ml.) was boiled under reflux for 3·5 hr. The product was added to water and extracted with ether, and the extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The residue was a pale green oil, which failed to yield crystals at −20°. When a portion was chromatographed on silica gel, 70% of the sample was recovered. The fractions (23%), obtained with 5 : 95 benzene–light petroleum, consisted of nearly pure 2-1′-isothiocyanatoethylnaphthalene, m. p. and mixed m. p. 49—50° after recrystallisation, with characteristic infrared absorption spectrum. Elution with 10 : 90 benzene–light petroleum then gave oils, and further elution with a 30 : 70 mixture gave partly crystalline fractions, from which 2-1′-thiocyanatoethylnaphthalene (13%) was obtained by crystallisation from light petroleum. The m. p. (48—49°) was a little low, but not depressed by authentic material, and the sample showed the characteristic thiocyanate band in the infrared absorption spectrum at 2160 cm.$^{-1}$. Distillation of the bulk of the reaction product yielded mainly 2-1′-ethoxyethylnaphthalene (see below), followed by a fraction which solidified and was fairly pure 2-1′-isothiocyanatoethylnaphthalene.

(*c*) Pure 2-1′-thiocyanatoethylnaphthalene (4·0 g.) was isomerised by four distillations under reduced pressure in a small-scale apparatus heated by a bath at 200°. The b. p. rose from ~140°/0·4 mm. and became practically constant at ~150°/0·4 mm. The distillate solidified and was purified by chromatography with 5 : 95 benzene–light petroleum on silica gel, which yielded 2·1 g. of 2-1′-isothiocyanatoethylnaphthalene, m. p. and mixed m. p. 48—50°.

(*d*) Solutions of pure 2-1′-isothiocyanatoethylnaphthalene in carbon tetrachloride showed a linear relationship between their concentration and the optical density of the strong, broad isothiocyanate band at 2096 cm.$^{-1}$ in the infrared absorption spectrum. This was used to

[35] Sheehan and Bolhofer, *J. Amer. Chem. Soc.*, 1950, **72**, 2786.
[36] Ing and Manske, *J.*, 1926, 2348.
[37] Ingersoll, Brown, Kim, Beauchamp, and Jennings, *J. Amer. Chem. Soc.*, 1936, **58**, 1808; cf. Moore, *Org. Reactions*, **5**, 301.

determine the amount of isothiocyanate formed by keeping samples of 2-1′-thiocyanatoethylnaphthalene for 1 hr. in stoppered tubes in a constant-temperature bath. At 120° the isothiocyanate content of the product was 73% and at 150° it was 77%; some decomposition occurred above ~120°. Similar experiments with 1-thiocyanatoethylbenzene [1] showed the content of 1-isothiocyanatoethylbenzene after 1 hr. to be 7% at 120°, and 42% at 150°.

2-1′-*Ethoxyethylnaphthalene*.—(*a*) The liquid fractions obtained by distillation of the mixed product from the reaction of 2-1′-chloroethylnaphthalene with ethanolic ammonium thiocyanate (see above) were redistilled, to give 2-1′-ethoxyethylnaphthalene, b. p. 111—113°/0·6 mm. (lit.,[38] 145—148°/16 mm.) (Found: C, 84·0; H, 7·7. Calc. for $C_{14}H_{16}O$: C, 84·0; H, 8·0%).

(*b*) A solution of 2-1′-bromoethylnaphthalene (2·0 g.) in ethanol (25 ml.) was refluxed for 12 hr. The distilled product was bromine-free and fairly homogeneous; redistillation afforded a sample of the 1′-ethoxide, b. p. 81—83°/0·25 mm.

(*c*) 2-1′-Thiocyanatoethylnaphthalene, b. p. >140°/0·4 mm. (see above), was treated with ethanol as in (*b*). Distillation afforded a sample of the 1′-ethoxide, b. p. 80—81°/0·15 mm.

2-*Isopropylnaphthalene*.—A poor yield was obtained by following a described method,[5] involving anhydrous aluminium chloride (40 g.), naphthalene (3 moles), and isopropyl bromide (2 moles), in the absence of a solvent; redistillation of the product gave 2-isopropylnaphthalene, b. p. 134·5—136°/14 mm. (lit.,[5] 130—135°/12 mm.). Alternatively, 2-acetylnaphthalene (see above; 1 mole) was converted by methylmagnesium iodide into 2-2′-naphthylpropan-2-ol (65%), which crystallised from light petroleum in prisms, m. p. 63—65° (lit.,[39] 65—65·5°). In a small-scale preparation, this alcohol (3·0 g.) was heated under reflux in ethanol with 4 times its weight of Raney nickel, as described for the reductive dehydroxylation of other alcohols; [22] 2-isopropylnaphthalene (65%), b. p. 137—139°/15 mm., was obtained on distillation.

Thiocyanation of 2-*Isopropylnaphthalene*.—(*a*) After prolonged reaction in acetic acid, as shown for expt. (vii) in Table 2, the crude product was isolated by addition to water, ether-extraction, and removal of solvent under reduced pressure. Passage of a solution of the product in 19 : 1 benzene–light petroleum down a column of silica gel removed resin, and distillation yielded 2-*isopropyl*-1-*thiocyanatonaphthalene* (1·1 g., 20%), a viscous, vesicant liquid, collected at 124—137°/0·02 mm.; a redistilled sample had b. p. 107°/3 × 10^{-4} mm. (Found: C, 74·0; H, 5·8; N, 6·3; S, 13·75. $C_{14}H_{13}NS$ requires C, 74·0; H, 5·7; N, 6·2; S, 14·1%). The infrared absorption spectrum (liquid film) showed a sharp peak at 2160 $cm.^{-1}$ characteristic of a thiocyanate. Reaction with excess of lithium aluminium hydride (1·8 mol.) yielded a liquid with a thiol-like odour, which gave only gum with 1-chloro-2,4-dinitrobenzene. No amine was detected in the reduction product. For the catalysed thiocyanation (expt. viii in Table 2; vol. of solution reduced to 125 ml.) the procedure was similar to that used by Söderbäck [20] for reactions with thiocyanogen. The aluminium chloride, dissolved in a few ml. of ether, was added to the 2-isopropylnaphthalene and thiocyanogen chloride in chloroform, and the mixture was briefly heated to 55° and left for 1·5 hr. at room temperature. Much yellow polymer was formed. The solution was washed with water and distilled; unchanged hydrocarbon was obtained, followed by 2-isopropyl-1-thiocyanatonaphthalene (1·1 g., 20%); the latter was redistilled at 112—113°/5 × 10^{-4} mm. and showed the same infrared spectral characteristics as the sample described above (Found: C, 73·9; H, 5·9; N, 6·2; S, 13·7%).

(*b*) Thiocyanation under the conditions given for expt. (ix) in Table 2, followed by removal of solvent below 40°, left a brown semi-solid residue, purified by elution through a column of silica gel with 1 l. of light petroleum. This yielded crude 2-*isothiocyanato*-2-2′-*naphthylpropane* as a liquid (2·0 g.) giving colourless prisms (0·5 g., 10%), m. p. 45—46°, by crystallisation from a light petroleum solution cooled to −20°; there was no depression in m. p. on admixture with a sample prepared as described below (Found: N, 6·2; S, 14·2. $C_{14}H_{13}NS$ requires N, 6·2; S, 14·1%). Neither the crude nor the purified product showed infrared spectral characteristics of a thiocyanate, but both showed the very strong, broad isothiocyanate band at 2078 $cm.^{-1}$ (5% carbon disulphide solution).

For comparison, 2-2′-naphthylpropan-2-ol (see above) was treated in benzene solution with dry hydrogen chloride, and solvent was removed under reduced pressure to yield 2-chloro-2-2′-naphthylpropane, which solidified on cooling and readily lost hydrogen chloride. Without

[38] Balfe, Kenyon, and Searle, *J.*, 1951, 380.
[39] Fieser and Chang, *J. Amer. Chem. Soc.*, 1942, **64**, 2043.

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purification, the chloride (0·15 mole) was treated with ammonium thiocyanate (0·45 mole) in acetone (200 ml.) at room temperature; ammonium chloride was immediately precipitated. After being left overnight, the solution was added to water, the mixture cooled, and the precipitated 2-isothiocyanato-2-2′-naphthylpropane recrystallised from light petroleum as prisms (23 g., 67%), m. p. 45·5—46°, which showed a strong broad band at 2070 cm.$^{-1}$ in the infrared absorption spectrum, but none attributable to thiocyanate. Treatment of the isothiocyanate with morpholine gave N-[N′-(1-*methyl*-1-2′-*naphthylethyl*)*thiocarbamoyl*]*morpholine*, recrystallising from benzene in prisms, m. p. 137·5—138·5° (Found: C, 69·0; H, 6·7; N, 8·7; S, 10·6. $C_{18}H_{22}N_2OS$ requires C, 68·8; H, 7·0; N, 8·9; S, 10·2%). By reduction of the isothiocyanate (2·0 g.) with lithium aluminium hydride (1·8 mol.), 2-*methylamino*-2-2′-*naphthylpropane* was obtained as a colourless liquid (1·46 g., 85%), b. p. 103°/0·2 mm. (Found: C, 84·9; H, 8·4; N, 7·0. $C_{14}H_{17}N$ requires C, 84·5; H, 8·4; N, 7·1%). With 1-naphthyl isocyanate, the amine gave the urea derivative, crystallising from chloroform in prisms, m. p. 190—192°.

Thiocyanation of t-Butylnaphthalene.—Reaction by a known method [6a] between naphthalene, t-butyl chloride, and anhydrous zinc chloride gave 2-t-butylnaphthalene in poor yield, b. p. 143—145°/27 mm. (lit.,[6a] 137—139°/17 mm.). Thiocyanation under the conditions given for expt. (x) in Table 2, followed by addition to water, extraction with ether, and distillation, gave 2-t-*butyl*-1-*thiocyanatonaphthalene* (1·75 g., 30%) as a pale yellow liquid, b. p. 140—142°/0·65 mm. (Found: C, 74·4; H, 6·3; N, 5·65; S, 12·8. $C_{15}H_{15}NS$ requires C, 74·7; H, 6·2; N, 5·8; S, 13·3%). The infrared absorption spectrum (liquid film) showed a fairly strong sharp peak at 2162 cm.$^{-1}$, due to thiocyanate. Reduction with lithium aluminium hydride (1·8 mol.) gave a liquid, with thiol-like odour, which formed only a gum in reaction with 1-chloro-2,4-dinitrobenzene.

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472. *Thiocyanogen, Thiocyanates, and Isothiocyanates. Part I. Homolytic Substitution in Arylalkyl Hydrocarbons by Thiocyanogen.*

By R. G. R. BACON and R. S. IRWIN.

Like thiocyanogen chloride, thiocyanogen undergoes homolysis in organic solvents when irradiated by a mercury-vapour lamp, and the resulting thiocyanogen radicals cause substitution of hydrogen on the α-carbon atom of arylalkyl hydrocarbons; the fastest reactions have been obtained in carbon tetrachloride. Toluene, 2-methylnaphthalene, ethylbenzene, 2-ethylnaphthalene, isobutylbenzene, and bibenzyl give thiocyanates; isopropylbenzene and diphenylmethane give thiocyanates which isomerise to isothiocyanates during isolation; from s-butylbenzene, triphenylmethane, 2-isopropylnaphthalene, and retene, only isothiocyanates are isolated. Aspects of S–S bond fission and of the isomerisation, R·SCN ⟶ R·NCS, are discussed. Decomposition to olefins is a property of some secondary and tertiary thiocyanates and isothiocyanates.

IN previous papers we have discussed properties of thiocyanogen monochloride,[1] thiocyanogen trichloride,[2] and various organic thiocyanates, isothiocyanates, or dichlorothiocyanates prepared by means of these reagents. Some observations made during this work have suggested directions in which the chemistry of the parent thiocyanogen, a compound well-known for its pseudohalogen character,[3,4] could be extended. During experiments

[1] Bacon, Guy, and Irwin, preceding paper.
[2] Bacon and Irwin, *J.*, 1960, 5079.
[3] Wood, *Org. Reactions*, 1946, **3**, 240.
[4] Kaufmann, in "Newer Methods of Preparative Organic Chemistry," Interscience Publ. Inc., New York, 1948.

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in which photo-initiated homolysis of thiocyanogen chloride was used for thiocyanation of the methyl group in 1-methylnaphthalene,[1] thiocyanogen was found to function similarly. As a result of such observations, it was suggested[5] that an important but previously unrecognised property of thiocyanogen is an ability to undergo homolysis, analogous to that of chlorine or bromine, giving thiocyanogen radicals: NCS·SCN ⟶ 2NCS·. The present paper describes the application of this property in the preparation of thiocyanates or isothiocyanates by substitution at the α-position in twelve arylalkyl hydrocarbons.

The thiocyanations, summarised in the Table, were carried out close to a 250 w mercury-vapour lamp. The energy emitted by this source included intense radiation at 365 mμ and less intense radiations at 302, 313, 334, and 405 mμ; absorption of light by solutions of thiocyanogen occurs from 400 to <280 mμ, with a maximum at 300 mμ.[6] Because of

Light-induced thiocyanation, by 0·1M-*thiocyanogen, at* 35°,[a] *of arylalkyl hydrocarbons:* Ar·CHRR′ ⟶ Ar·CRR′·SCN *or* Ar·CRR′·NCS.

Hydrocarbon	Hydrocarbon (mol.) per mol. of $(SCN)_2$	Solvent	Reaction time (hr.)	Total $(SCN)_2$ decomp. (%) [b]	$(SCN)_2$ (%) accounted for by isolated product [c]	Product
None	—	CCl_4	3	2	—	—
Ph·CH_3 (i)	10	,,	3·5	60	31	Thiocyanate
(ii)	5	AcOH	4·5	12	7	,,
(iii)	100	PhMe	2·5	87	49	,,
Ph·CH_2Me (i)	5	CCl_4	1·5	98	89	,,
(ii)	,,	AcOH	3·0	54	34	,,
Ph·$CHMe_2$ (i)	,,	CCl_4	0·5	97	82	Isothiocyanate
(ii)	,,	AcOH	3·0	47	18	,,
Ph·CMe_3	,,	CCl_4	2·5	5	—	None
Ph·CH_2Pr^i	4	,,	3·0	83	70	Thiocyanate
Ph·CHMeEt	,,	,,	1·25	98	58	Isothiocyanate
2-$C_{10}H_7$·CH_3	5	,,	6·0	64	25	Thiocyanate
2-$C_{10}H_7$·CH_2Me	,,	,,	2·5	95	51	,,
2-$C_{10}H_7$·$CHMe_2$	0·5	,,	2·3	64	5 [d]	Isothiocyanate
2-$C_{10}H_7$·CMe_3	2	,,	2·0	5	—	None
Ph·CH_2·CH_2Ph	1	,,	3·5	74	61	Thiocyanate
CH_2Ph_2	5	,,	3·0	91	49	Isothiocyanate
$CHPh_3$	1	,,	0·5	90	77	,,
Retene	0·5	,,	4·0	50	15 [e]	,,

[a] Volume of solutions, 500 ml.; variation in concentration, 0·079 to 0·123M; variation in temperature, 32—38°. [b] From iodometric titration. [c] This is also the yield (%) of purified product, except when thiocyanogen was in excess; cf. *d* and *e*. [d] Yield calculated on hydrocarbon, 10%; for the chromatographed product before crystallisation, the yield calculated on hydrocarbon was 56%. [e] Yield calculated on hydrocarbon, 29%.

thermal radiation from the lamp, it was convenient to conduct reactions at ~35°. Under such conditions, solutions (~0·1M) of thiocyanogen in carbon tetrachloride declined in iodometric titre at the rate of about 1% in 1—2 hr., and formed the customary precipitate of polymer. The rate of decomposition was nearly the same for thiocyanogen solutions containing t-butylbenzene or 2-t-butylnaphthalene, which, having no α-hydrogen atoms, do not undergo homolytic thiocyanation.[1] This degree of stability was unexpected, in view of reports[3] of the ready polymerisation of thiocyanogen by sunlight.

The overall reaction with arylalkyl hydrocarbons is:

$$Ar{\cdot}CHRR' + (SCN)_2 \longrightarrow Ar{\cdot}CRR'{\cdot}SCN \text{ (or } Ar{\cdot}CRR'{\cdot}NCS) + HSCN$$

Yields of purified products varied from about 10% to 90%, after reaction periods of 0·5—6 hr.; in most cases we employed an excess of the hydrocarbon and continued irradiation

[5] Bacon, Guy, Irwin, and Robinson, *Proc. Chem. Soc.*, 1959, **304**; Bacon, "Thiocyanates, Thiocyanogen, and Related Compounds," in "Organic Sulphur Compounds," Pergamon Press, London, Vol. I, in the press.

[6] Bacon and Irwin, *J.*, 1958, 778.

until the reagent was substantially consumed, as shown by iodometric titration, but we did not ascertain conditions for obtaining optimum yields. There were differences of 10—40% between the total amount of reagent decomposed, determined iodometrically, and the amount which had caused substitution, indicated by yields of purified products. Such differences could be due, in varying degree, to polymerisation of the reagent, to side reactions, and to decomposition of thiocyanation products (see below) or difficulties in their isolation. Chromatography removed resins, but crystalline or liquid products, other than those listed, were not isolated. The reasonably good stability of thiocyanogen when irradiated suggests that polymer-formation accompanying thiocyanation should have been relatively unimportant, but this is uncertain, since little is known about catalysis of the polymerisation, or indeed of its chemical nature. Thiocyanic acid, produced in the thiocyanations, is an additional source of polymer.

We suggest that the substitution involves radical-chain reactions of the type well known for photo-initiated halogenation:

$$(SCN)_2 \xrightarrow{h\nu} 2\cdot SCN \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Ar\cdot CHRR' + \cdot SCN \longrightarrow Ar\cdot CRR'\cdot + HSCN \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$Ar\cdot CRR'\cdot + (SCN)_2 \longrightarrow Ar\cdot CRR'\cdot SCN + \cdot SCN \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$(? \text{ or } Ar\cdot CRR'\cdot NCS)$$

etc.,

followed in some cases by:

$$Ar\cdot CRR'\cdot SCN \longrightarrow Ar\cdot CRR'\cdot NCS \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Step (1) is the homolysis of the disulphide bond of thiocyanogen, giving resonance-stabilised radicals:

$$NCS{-}SCN \longrightarrow 2(N{\equiv}C{-}S\cdot \longleftrightarrow \cdot N{=}C{=}S)$$

It has been concluded, from recent studies of S–S bonds in disulphides,[7,8] that their homolysis requires a temperature of about 140°, unless effected by irradiation, or by reaction with other radicals, in which case ordinary temperatures suffice. Evidence given for the photo-initiated homolysis concerns the capacity of the resulting thiyl radicals to cause polymerisation of vinyl compounds and dienes,[9] to accelerate radical-type addition of a thiol to vinyl compounds,[10] and to react with hydrogen-donors and with 1,1-diphenyl-2-picrylhydrazyl.[11] Dialkyl disulphides are not so effective for such purposes as diaryl disulphides, thiuram disulphides, or di(benzothiazol-2-yl) disulphide, all of which produce resonance-stabilised radicals. In thiocyanogen radicals, such stabilisation is due to the constituent cyano-group, in which respect there is a parallel with cyanoalkyl radicals, which are formed readily from azonitriles by heat,[12] or by irradiation from a mercury-vapour lamp:[13]

$$NC\cdot CR_2\cdot N{:}N\cdot CR_2\cdot CN \longrightarrow 2(\cdot CR_2{-}C{\equiv}N \longleftrightarrow CR_2{=}C{=}N\cdot) + N_2$$

Two examples of side-chain thiocyanation of arylalkyl hydrocarbons by thiocyanogen are in the literature. The reaction of 3-methylcholanthrene[14] with thiocyanogen in carbon tetrachloride, presumably influenced by daylight, did not occur in the tetracyclic aromatic ring system, but in a methylene group: $-CH_2\cdot CH_2- \longrightarrow -CH_2\cdot CH(SCN)-$. This

[7] Moore, *J.*, 1952, 4232.
[8] Bateman, Moore, and Porter, *J.*, 1958, 2866.
[9] Birch, Cullum, and Dean, *J. Inst. Petroleum*, 1953, **39**, 206; Kharasch, Nudenberg, and Meltzer, *J. Org. Chem.*, 1953, **18**, 1233; Otsu, *J. Polymer Sci.*, 1956, **21**, 559.
[10] Rueggeberg, Cook, and Reid, *J. Org. Chem.*, 1948, **13**, 110; Rueggeberg, Chernack, Rose, and Reid, *J. Amer. Chem. Soc.*, 1948, **70**, 2292.
[11] Schaafsma, Bickel, and Kooyman, *Tetrahedron*, 1960, **10**, 76.
[12] Reviewed by Walling, in "Free Radicals in Solution," Wiley and Sons, New York, 1957.
[13] Lewis and Matheson, *J. Amer. Chem. Soc.*, 1949, **71**, 747; Back and Sivertz, *Canad. J. Chem.*, 1954, **32**, 1061.
[14] Wood and Fieser, *J. Amer. Chem. Soc.*, 1941, **63**, 2323.

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recalls the influence of daylight in promoting substitution of the methyl group when methylnaphthalenes react with thiocyanogen chloride.[1] A second example,[15] which we repeated (see Table), is the thiocyanation of the isopropyl group in 7-isopropyl-1-methylphenanthrene (retene), but in this case a mercury-vapour lamp was employed.

More numerous in the literature,[3] and strongly suggestive of a radical mechanism, are cases of light-promoted reactions of thiocyanogen with olefins. In a re-examination [5,16] of this aspect of thiocyanation, we find it to be more complicated than has been reported, and highly sensitive to variations in experimental conditions. The reaction with arylalkyl hydrocarbons is apparently less sensitive, but a preliminary examination of experimental variables has shown a solvent effect; acetic acid consistently proved inferior to carbon tetrachloride, and, in a series of thiocyanations carried out with isopropylbenzene, the rate of consumption of the reagent in a series of solvents was: $CCl_4 > CHCl_3 > C_6H_6 > EtBr > Et_2O > PhNO_2 > AcOH$. The trend thus displayed is the reverse of that observed [17] for heterolytic thiocyanation of an aromatic nucleus by thiocyanogen chloride.

Comparison of data in the Table suggests that, as might be expected, ease of replacement of hydrogen is in the order, tertiary > secondary > primary α-carbon atom. In retene it is the isopropyl, not the methyl group, which is thiocyanated. However, precise comparisons are difficult to make, since some of the tertiary and secondary arylalkyl derivatives readily undergo elimination reactions, like those of the corresponding halides. Olefins thus formed from isopropyl-substituted hydrocarbons probably polymerise, but, in the thiocyanation of s-butylbenzene, the resulting 2-isothiocyanato-2-phenylbutane was accompanied by 2-phenylbut-2-ene: $Ph{\cdot}CMeEt{\cdot}NCS \longrightarrow Ph{\cdot}CMe{:}CHMe + HSCN$. A similar elimination, giving stilbene, occurred spontaneously in the secondary thiocyanato-derivative isolated from bibenzyl: $Ph{\cdot}CH_2{\cdot}CHPh{\cdot}SCN \longrightarrow Ph{\cdot}CH{:}CHPh + HSCN$.

The response of the hydrocarbons to thiocyanation should be governed by the relative ease of hydrogen-abstraction in step (2) of the reaction scheme given above. Isolation of an isothiocyanate instead of a thiocyanate could be due, in step (3), to interaction of the resulting arylalkyl radical with a nitrogen atom of thiocyanogen, instead of with a sulphur atom: $NCS{\cdot}S{\cdot}C{:}N + {\cdot}CR_3 \longrightarrow NCS{\cdot} + S{:}C{:}N{\cdot}CR_3$. Alternatively, the initial product could be a thiocyanate which spontaneously isomerises (step 4). In two cases, the crude product was shown to contain an unstable thiocyanate which underwent complete conversion into an isothiocyanate during isolation. For four other cases, where only an isothiocyanate was observed, an initially formed thiocyanate could reasonably have been expected to isomerise at the temperature of the reaction. The result depends essentially on the structure of the hydrocarbon, as appears in the following summary (thiocyanates isomerising during isolation are shown in parentheses):

(i) Hydrogen replaced on a primary α-carbon atom:
$Ph{\cdot}CH_3$, $C_{10}H_7{\cdot}CH_3 \longrightarrow$ thiocyanate
(ii) Hydrogen replaced on a secondary α-carbon atom:
$Ph{\cdot}CH_2Me$,* $C_{10}H_7{\cdot}CH_2Me$,* $Ph{\cdot}CH_2Pr^i$, $Ph{\cdot}CH_2{\cdot}CH_2Ph \longrightarrow$ thiocyanate
CH_2Ph_2 ($\longrightarrow$ thiocyanate) $\longrightarrow$ isothiocyanate
(iii) Hydrogen replaced on a tertiary α-carbon atom:
$Ph{\cdot}CHMe_2$ ($\longrightarrow$ thiocyanate) $\longrightarrow$ isothiocyanate
$Ph{\cdot}CHMeEt$, $CHPh_3$, $C_{10}H_7{\cdot}CHMe_2$, $C_{14}H_8Me{\cdot}CHMe_2 \longrightarrow$ isothiocyanate
(* The derived thiocyanate was previously shown [1] to isomerise at or above 120°.)

Hence, production of an isothiocyanate is aided by (*a*) a secondary carbon atom, or preferably a tertiary carbon atom, at the reaction centre, (*b*) the attachment, at this centre, of aryl groups rather than alkyl groups, (*c*) the attachment, at this centre, of polycyclic

[15] Frederiksen and Liisberg, *Acta Chem. Scand.*, 1951, **5**, 621.
[16] Bacon and Robinson, unpublished investigations.
[17] Bacon and Guy, *J.*, 1960, 318.

aryl groups (*e.g.*, naphthyl, phenanthryl) rather than phenyl groups. Even the primary group $-CH_2 \cdot SCN$, when attached to the benzanthracene ring system, is converted into $-CH_2 \cdot NCS$ at 100°.[14]

The type of product obtained on thiocyanation is readily distinguished, as was shown previously,[1] by chemical methods and by infrared spectroscopy; differences in the absorption bands due to –SCN and –NCS groups have recently been discussed exhaustively.[18] For eight of the hydrocarbons in the Table, essential characterisation had already been carried out when thiocyanogen chloride, which gives the same products as thiocyanogen, was used for homolytic substitution.[1,19] Among these hydrocarbons, isopropylbenzene gives a thiocyanate which isomerises during isolation. When thiocyanation was carried out with thiocyanogen chloride,[19] the product, isolated by distillation, was the isothiocyanate. The product here described was shown by infrared spectroscopy to contain a major proportion of the thiocyanate before distillation. The thiocyanate was also present, though in smaller proportion, in the undistilled product of reaction between diphenylmethyl chloride and ammonium thiocyanate in acetone at room temperature. The crude thiocyanation product gave an unstable thiol with lithium aluminium hydride, while the distilled product gave the readily characterised methylamino-compound when similarly reduced, and it gave an adduct with morpholine. Diphenylmethane and thiocyanogen likewise gave the thiocyanato-derivative, which changed into the isothiocyanate when excess of the hydrocarbon was removed by distillation. The same behaviour has been reported for the product obtained with thiocyanogen chloride.[19] A direct preparation of the isothiocyanate from diphenylmethylamine [20] confirms its constitution.

The case of triphenylmethane also requires comment, since thiocyanogen, like thiocyanogen chloride,[19] gave a product identical with that wrongly described in the literature as triphenylmethyl thiocyanate. From the known influence of structural factors (see above), thiocyanation would be expected to give exclusively triphenylmethyl isothiocyanate, and this in fact had been shown by infrared spectral characteristics.[19] Supporting chemical evidence could also be given, but this is unnecessary, since the structure has recently been discussed by Iliceto and his co-workers,[21] who reached the same conclusion as we did.

Thiocyanation of isobutylbenzene, s-butylbenzene, bibenzyl, and retene had not been carried out with thiocyanogen chloride. The products obtained with thiocyanogen were characterised in the usual way and were compared, in the first three cases, with samples obtained by the customary preparative method, namely, treatment of the corresponding arylalkyl halide with an alkali-metal thiocyanate in an organic solvent. The structure of the halide is the main influence determining whether the product isolated is a thiocyanate, an isothiocyanate, or (*e.g.*, for $Ph \cdot CMe_2X$, $CHPh_2X$, $C_{10}H_7 \cdot CHMeX$) a mixture of the two. If the isothiocyanates obtained by homolytic thiocyanation of the hydrocarbons are due to isomerisation of initially formed thiocyanates, some correspondence with the products of the halide reactions is not surprising; isomerisation is currently attributed to the formation (from R–SCN) and the recombination (giving R–NCS) of carbonium and thiocyanate ions,[21,22] which are likewise involved in S_N1 reactions of secondary and tertiary arylalkyl halides with alkali-metal thiocyanates.

Experimental

Thiocyanation Procedure.—Solutions of thiocyanogen (~0·1M) were prepared from bromine and an excess of lead thiocyanate, as previously described, in "AnalaR" carbon

[18] Caldow and Thompson, *Spectrochim. Acta*, 1958, **13**, 212; Lieber, Rao, and Ramachandran, *ibid.*, 1959, **13**, 296; Ham and Willis, *ibid.*, 1960, **16**, 279, 393; Svatek, Zahradnik, and Kjaer, *Acta Chem. Scand.*, 1959, **13**, 442.

[19] Bacon and Guy, *J.*, 1961, 2428.

[20] Kaye, Kogon, and Parris, *J. Amer. Chem. Soc.*, 1952, **74**, 403.

[21] Iliceto, Fava, and Mazzuccato, *J. Org. Chem.*, 1960, **25**, 1445.

[22] Iliceto, Fava, and Mazzuccato, *Tetrahedron Letters*, 1960, No. 11, 27; Smith and Emerson, *J. Amer. Chem. Soc.*, 1960, **82**, 3076.

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tetrachloride,[23] or in acetic acid which had previously been refluxed with 5% of acetic anhydride for 4 hr.[16] The required amount of hydrocarbon was dissolved in a measured amount of thiocyanogen solution in a Pyrex flask, and the mixture was gently stirred while being irradiated with a 250 w "Mazda" ME/D box-type lamp, set at 8 cm. from the wall of the flask. A water-cooled tube inserted into the flask moderated the effect of thermal radiations and kept the solution at an average temperature of 35°. Consumption of thiocyanogen was measured by iodometric titration of aliquot parts.

At the end of a reaction, precipitated polymeric thiocyanogen was removed by filtration, and unchanged reagent was destroyed by dilution with a large excess of water, in the case of acetic acid solutions, or by shaking with water, in the case of carbon tetrachloride solutions. Crude product was then isolated by ether-extraction or by evaporation, respectively, and was purified by chromatography on silica gel with mixtures of light petroleum and benzene.

Some variations in conditions were examined for the reaction of isopropylbenzene (0·05M) with thiocyanogen (0·10M) in carbon tetrachloride. The distance between the flask and the lamp strongly influenced reaction rate; *e.g.*, at 25 cm. 75 min. were required for 50% decomposition of thiocyanogen at 20°, while at 50 cm. 200 min. were required. Relatively small increases in rate resulted from using a quartz instead of a Pyrex flask, or by using a white-walled box in place of the dark-walled box which normally surrounded the apparatus. The effect of variation in the solvent was tested at 20°, with 25 cm. between the lamp and flask; approximate times for 50% decomposition of the thiocyanogen were then: in carbon tetrachloride, 75 min.; in chloroform, 80 min.; in benzene, 100 min.; in ethyl bromide, 115 min.; in diethyl ether, 120 min.; in nitrobenzene, 40% in 200 min.; in acetic acid (containing 5% of acetic anhydride), 20% in 300 min. These times include variable initial periods of ~5 to ~20 min., during which there was negligible reaction, but the slopes of the approximately straight lines, observed for the time–reagent concentration relationship below 50% followed the same order.

The products referred to in the following paragraphs were obtained under conditions summarised in the Table.

Toluene.—After removal of unchanged reagent and solvent, the products from expts. (i)—(iii) with toluene were purified from resinous contaminants by chromatography with 3 : 2 benzene–light petroleum on silica gel. Recrystallisation of the benzyl thiocyanate from ethanol gave needles, m. p. and mixed m. p. 40°.

Ethylbenzene.—The crude reaction products (i) and (ii) were purified by distillation to give 1′-thiocyanatoethylbenzene, b. p. 137—139°/11 mm., n_D^{25} 1·5615, which gave an infrared absorption spectrum identical with that of the samples previously described.[19] 1′-Isothiocyanatoethylbenzene, prepared for comparison by reaction of styrene with sodium thiocyanate in aqueous sulphuric acid,[24] was a lachrymatory and vesicant liquid, b. p. 86°/0·8 mm., n_D^{25} 1·5770, with a broad, strong infrared absorption band at 2094 cm.$^{-1}$.

Isopropylbenzene.—(*a*) The crude products from the thiocyanation of isopropylbenzene, freed from solvent at <45°, showed a strong sharp peak in the infrared absorption spectrum at 2165 cm.$^{-1}$, due to a major proportion of 2-phenyl-2-thiocyanatopropane, and showed a weak, broad band at ~2080 cm.$^{-1}$, due to a minor proportion of 2-isothiocyanato-2-phenylpropane. Reduction with lithium aluminium hydride [19] of products obtained in this way yielded a liquid thiol (*e.g.*, 66%), with characteristic odour, which decomposed when distillation was attempted. Conversion of the thiol into a 2,4-dinitrophenyl sulphide was unsuccessful; treatment in ethanolic solution with silver nitrate, mercuric chloride, or lead acetate gave precipitates of metal derivatives which were unstable; oxidation by air or iodine gave an impure, colourless, crystalline disulphide.

(*b*) Treatment of 2-chloro-2-phenylpropane with ammonium thiocyanate in acetone [19] was carried out for 1 hr. at room temperature; this sufficed to give a 58% yield of the 1′-isothiocyanate on distillation. After removal of solvent from the crude product at <40°, the infrared absorption spectrum of the residue indicated the presence of a minor proportion of thiocyanate and a major proportion of isothiocyanate. On distillation, the products obtained by methods (*a*) or (*b*) underwent complete conversion into 2-isothiocyanato-2-phenylpropane,[19] b. p. 72°/0·2 mm., n_D^{25} 1·5682, which became yellow and deposited resin when kept. Reduction of the isothiocyanate with lithium aluminium hydride [1] gave *2-methylamino-2-phenylpropane* (63%), b. p. 93°/19 mm. (Found: C, 80·2; H, 10·0; N, 9·8. $C_{10}H_{15}N$ requires C, 80·5; H, 10·1;

[23] Angus and Bacon, *J.*, 1958, 774.
[24] Luskin, Gantert, and Craig, *J. Amer. Chem. Soc.*, 1956, **78**, 4965.

N, 9·4%). The amine and 1-naphthyl isocyanate gave N-*methyl*-N-(2-*phenyl*-2-*propyl*)-N′-1′-*naphthylurea*, obtained in needles (from ethanol), m. p. 136—137° (Found: C, 79·0; H, 6·45; N, 8·7. $C_{21}H_{22}N_2O$ requires C, 79·3; H, 6·9; N, 8·8%). The isothiocyanate and morpholine reacted immediately in acetone to give N-[N′-(2-*phenyl*-2-*propyl*)*thiocarbamoyl*]*morpholine*, which crystallised from light petroleum in needles, m. p. 145° (Found: C, 63·8; H, 7·1; N,10·35; S, 12·3. $C_{14}H_{20}N_2OS$ requires C, 63·6; H, 7·6; N, 10·6; S, 12·1%).

Isobutylbenzene.—The thiocyanation product, purified by distillation, gave 2-*methyl*-1-*phenyl*-1-*thiocyanatopropane* (70%), b. p. 77°/0·1 mm., which was pleasant in odour and showed a strong, sharp peak at 2159 cm.$^{-1}$ in the infrared absorption spectrum (Found: C, 69·4; H, 7·1; N, 7·35; S, 16·6. $C_{11}H_{13}NS$ requires C, 69·1; H, 6·8; N, 7·3; S, 16·75%). For comparison, 2-methyl-1-phenylpropan-1-ol was treated in benzene with dry hydrogen chloride to give 1-chloro-2-methyl-1-phenylpropane, a pleasant-smelling liquid, b. p. 37°/0·1 mm., and this, without distillation, was kept under reflux for 1 hr., and then at room temperature for 12 hr., with ammonium thiocyanate (6 mol.) in acetone. Distillation yielded unchanged chloro-compound, and then 2-methyl-1-phenyl-1-thiocyanatopropane (24%), b. p. 114°/1·6 mm. Reduction of the thiocyanate with lithium aluminium hydride [19] gave 2-methyl-1-phenylpropane-1-thiol, which failed to form the 2,4-dinitrophenyl sulphide but reacted with a 20% solution of lead acetate in 1 : 1 aqueous ethanol to give the yellow *lead salt*, recrystallising from ethanol as prisms, m. p. 148—150° (Found: C, 45·2; H, 4·6; S, 11·8. $C_{20}H_{26}PbS_2$ requires C, 44·7; H, 4·8; S, 11·9%).

s-Butylbenzene.—Distillation of the crude thiocyanation product gave a little 2-phenylbut-2-ene, b. p. 24—28°/0·07 mm., 186°/1 atm., n_D^{25} 1·5395 (Cram [25] gives b. p. 194°, n_D^{25} 1·5393, for the *cis*-isomer, and b. p. 174°, n_D^{25} 1·5192, for the *trans*-isomer). This was followed by 2-*isothiocyanato*-2-*phenylbutane* (58%), b. p. 82—83°/0·07 mm. (Found: C, 69·4; H, 7·05; N, 7·4; S, 16·5. $C_{11}H_{13}NS$ requires C, 69·1; H, 6·8; N, 7·3; S, 16·75%). The isothiocyanate showed a strong, broad infrared band at 2100 cm.$^{-1}$; it possessed similar instability to 2-isothiocyanato-2-phenylpropane; and it gave a morpholine adduct, N-[N′-(2-*phenyl*-2-*butyl*)-*thiocarbamoyl*]*morpholine*, which crystallised from light petroleum in needles, m. p. 107° (Found: C, 65·1; H, 7·5; N, 9·9; S, 11·2. $C_{15}H_{22}N_2OS$ requires C, 64·8; H, 7·9; N, 10·1; S, 11·5%). For comparison, 2-phenylbutan-2-ol [26] was converted into 2-chloro-2-phenylbutane by treatment in light petroleum with dry hydrogen chloride. Washing with aqueous sodium hydrogen carbonate and removal of solvent under reduced pressure left the chloro-compound as a liquid which readily lost hydrogen chloride if warmed. This was treated with ammonium thiocyanate (3 mol.) in acetone, for 1 hr. at room temperature, and the product, after dilution, ether-extraction, and treatment with sodium hydrogen carbonate, was distilled, yielding 2-phenylbut-2-ene (40%) and 2-isothiocyanato-2-phenylbutane (34%), b. p. 87—88°/0·2 mm., which was identical in properties with the sample described above.

2-*Methyl*-, 2-*Ethyl*-, *and* 2-*Isopropyl*-*naphthalene*.—The products from the thiocyanations were purified by chromatography, as described for corresponding samples obtained with thiocyanogen chloride.[1] The total weights of purified fractions amounted to 60—70% of the crude products added to the column. There were resinous impurities which resisted elution, particularly in the case of the product from 2-isopropylnaphthalene. As indicated in note (*d*) in the Table, the low yield recorded for the pure product from this hydrocarbon was due to difficulty in inducing crystallisation of the liquid isothiocyanate fractions, which were eluted from the column in substantial amount. 2-Thiocyanatomethylnaphthalene, m. p. and mixed m. p. 101°, 2-1′-thiocyanatoethylnaphthalene, m. p. and mixed m. p. 52·5°, and 2-isothiocyanato-2-2′-naphthylpropane, m. p. and mixed m. p. 46°, were thus obtained. Their structures were checked by infrared spectroscopy.

Bibenzyl.—By chromatography of the crude thiocyanation product on silica gel with 1 : 4 benzene–light petroleum, or by direct distillation of the crude product at the pressure of a mercury diffusion pump, 1,2-*diphenylethyl thiocyanate* was obtained as a colourless liquid, b. p. 127°/4 × 10^{-3} mm., some samples of which solidified, giving prisms, m. p. 35—36·5° after recrystallisation from methanol (Found: C, 75·4; H, 5·3; N, 5·9; S, 13·15. $C_{15}H_{13}NS$ requires C, 75·3; H, 5·4; N, 5·9; S, 13·4%). It showed a strong, sharp peak at 2165 cm.$^{-1}$. Distillation was accompanied by decomposition to polymeric thiocyanic acid and *trans*-stilbene, m. p. 124° after recrystallisation from ethanol. Similar decomposition occurred readily when

[25] Cram, *J. Amer. Chem. Soc.*, 1949, **71**, 3883.
[26] Klages, *Ber.*, 1902, **35**, 3507.

a sample of the thiocyanate was stored at room temperature. A sample thrice distilled under reduced pressure at 160° contained <5% of isothiocyanate, as judged by a weak band at 2080 cm.$^{-1}$.

To obtain the compound by an alternative route, 1,2-diphenylethanol,[27] m. p. 68°, was treated in benzene with dry hydrogen bromide, to give 1,2-diphenylethyl bromide,[28] a liquid which underwent dehydrobromination if heated; solvent was removed at <40°. The bromide was kept for 15 hr. at room temperature, in acetone solution, with ammonium thiocyanate (3 mol.). 1,2-Diphenylethyl thiocyanate was isolated (90%) by dilution with water and ether-extraction, and was purified by brief warming with active charcoal, followed by elution from a column of silica gel with 3 : 17 benzene–light petroleum.

The thiocyanate, prepared by either route, was converted by reaction with lithium aluminium hydride [19] into 1,2-diphenylethanethiol (87%), m. p. 29—31°, b. p. 110°/0·25 mm. (lit., m. p. 41°,[29] b. p. 146—148°/4 mm.[30]) (Found: C, 78·8; H, 6·75; S, 14·6. Calc. for $C_{14}H_{14}S$: C, 78·5; H, 6·55; S, 14·9%). This was converted into 2,4-dinitrophenyl 1,2-diphenylethyl sulphide, obtained from ethanol in yellow plates, m. p. 109° (lit.,[29] 108—109°) (Found: C, 63·3; H, 4·3; N, 7·6; S, 8·6. Calc. for $C_{20}H_{16}N_2O_4S$: C, 63·2; H, 4·2; N, 7·6; S, 8·4%). When equimolecular proportions of 1,2-diphenylethyl thiocyanate and thiocyanogen were irradiated for 90 min. in carbon tetrachloride at 30°, only 0·09 mol. of the reagent was consumed, 92% of the thiocyanate was recovered by chromatography, and no dithiocyanate was detected.

Diphenylmethane.—After removal of solvent from the thiocyanation product at <50°, the residual pale yellow liquid showed a sharp infrared peak at 2160 cm.$^{-1}$, due to thiocyanate, but no band due to isothiocyanate. Removal of excess of diphenylmethane by distillation at 78°/0·08 mm. caused isomerisation, since chromatography of the residue with 1 : 9 benzene–light petroleum gave diphenylmethyl thiocyanate (49%), which crystallised from light petroleum as prisms, m. p. 57° (lit.,[20] 56·5—57·5°), not depressed on admixture with the sample obtained [19] with thiocyanogen chloride. With morpholine it gave N-(*N'-diphenylmethylthiocarbamoyl*)*morpholine*, which crystallised from ethanol in needles, m. p. 152—153° (Found: C, 69·5; H, 6·2; N, 9·2; S, 10·1. $C_{18}H_{20}N_2OS$ requires C, 69·2; H, 6·4; N, 9·0; S, 10·3%). For comparison, diphenylmethyl bromide, b. p. 136°/1·2 mm., was prepared (80%) by bromination of diphenylmethane [31] and was treated with ammonium thiocyanate (3 mol.) in refluxing acetone for 30 min. Infrared spectroscopic examination of the crude product showed the presence of both thiocyanate and isothiocyanate groups. The mixture was heated at 100° for 2 hr. and treated in light petroleum with morpholine, which yielded the derivative of the isothiocyanate, m. p. and mixed m. p. 152°.

Triphenylmethane.—The crude reaction product showed only the very strong band at 2050 cm.$^{-1}$ in the infrared absorption spectrum, due to isothiocyanate. The recrystallised product, m. p. 138° (lit.,[21] 138—138·5°), was identical with that obtained by using thiocyanogen chloride as the reagent,[19] or by treating triphenylmethyl chloride with ammonium thiocyanate in acetone.

Retene.—Abietic acid (from colophony [32]) was heated with palladium–charcoal [33] to afford retene, m. p. 94—97° after one recrystallisation from ethanol (lit.,[33] 100·5—101°). When solvent was removed from the thiocyanation product at <40°, the crude residue showed a strong broad band at 2055 cm.$^{-1}$ due to the isothiocyanate group, but no peak due to thiocyanate. Recrystallisation from ethanol yielded 2-isothiocyanato-2-1'-methyl-7'-phenanthrylpropane as prisms, m. p. 103—106° (lit.,[15] 107·5—108°) (Found: C, 78·6; H, 5·9; N, 4·85; S, 10·7. Calc. for $C_{19}H_{17}NS$: C, 78·3; H, 5·8; N, 4·8; S, 11·2%). It gave the corresponding thiosemicarbazide with hydrazine, m. p. 186—187° (lit.,[15] 188—189°). Reduction with lithium aluminium hydride gave 2-1'-methyl-2-methylamino-7'-phenanthrylpropane, which was converted by 1-naphthyl isocyanate into *N-methyl*-N-2-(2-1'-*methyl*-7'-*phenanthryl*)*propyl*-N'-1''-*naphthylurea*, difficult to purify and obtained as prisms, m. p. 196·5—198° (Found: C, 82·4; H, 6·0; N, 7·0. $C_{30}H_{28}N_2O$ requires C, 83·3; H, 6·5; N, 6·5%).

THE QUEEN'S UNIVERSITY, BELFAST. [*Received, December 22nd*, 1960.]

[27] Tout and Guyard, *Bull. Soc. chim. France*, 1947, 1086.
[28] Curtin and Kellom, *J. Amer. Chem. Soc.*, 1953, **75**, 6011.
[29] Pascual Teresa and Sánchez Bellido, *Anales real Soc. espan. Fis. Quim.*, 1954, **50**, *B*, 71.
[30] Hauser, Kantor, and Brasen, *J. Amer. Chem. Soc.*, 1953, **75**, 2660.
[31] Morris, Thomas, and Brown, *Ber.*, 1910, **43**, 2957.
[32] *Org. Synth.*, 1952, **32**, 1.
[33] Ruzicka and Waldmann, *Helv. Chim. Acta*, 1933, **16**, 842.

473. *Volatile Products of Pyrolysis of Nicotine.**

By Charles H. Jarboe and C. James Rosene.

The pyrolysis of nicotine in an inert atmosphere at 600—900° produces a variety of heterocyclic nitrogen compounds and aromatic hydrocarbons, consideration of which permits a mechanism to be established for the primary reactions. In addition, a number of secondary products are ascribed to free-radical reactions involving cleavage and recombination.

It is well known that only a part of the nicotine present in tobacco is transported into tobacco smoke, and more than 30 bases structurally related to nicotine have been identified in smoke.[1] When nicotine is passed through heated packed reactors [2] the products of pyrolysis include hydrogen cyanide, methylamine, ethylamine, pyridine, 3-picoline, 3-ethylpyridine, 3-vinylpyridine, nicotinic acid, myosmine, nicotyrine; noteworthy is its catalytic pyrolysis to 3-cyanopyridine in 51·5% yield.[3] Percolation through tobacco ashes at 740° has been found by Truhart *et al.*[2] to produce, in addition to the above compounds, nicotinamide, nornicotyrine, *N*-methylmyosmine, nornicotine, and tentatively a pyridinealdehyde and an aminopyridine. At 750° nicotine pyrolysis yields also dibenzo-[*a*,*j*]- and -[*a*,*h*]-acridine;[4] these compounds and dibenzo[*c*,*g*]carbazole have been found in cigarette smoke and are considered possible nicotine artifacts. As the conditions in these experiments were relatively uncontrolled and in many cases air was the carrier, both oxidation and thermal reactions may have been involved.

Table 1. *Pyrolysis products of nicotine.**

Compound	Retention time † "Ucon"	Retention time † "Carbowax"	Temperature 600°	700°	800°	900°
Pyridine	1·00	1·00	0·50	3·40	6·00	4·70
3-Picoline	1·64	1·46	1·40	4·00	2·60	0·05
3-Ethylpyridine	2·15	1·92	1·10	0·46	0·03	0·03
3-Vinylpyridine	2·82	2·42	10·00	8·00	2·60	0·03
Metanicotine	—	2·46	0·01	0·01	0·01	—
Benzonitrile	4·10	3·61	—	—	0·01	0·44
3-Cyanopyridine	5·50	5·43	0·64	1·80	1·10	0·05
Naphthalene	6·85	5·46	—	—	0·01	0·45
Compound A	—	4·24	0·11	0·10	0·13	—
3-(Buta-1,3-dienyl)pyridine	—	5·96	0·17	0·01	—	—
2-Cyanopyridine	9·40	8·31	—	—	0·01	0·01
Compound B	10·6	8·65	—	0·41	—	—
Quinoline	12·1	9·82	0·01	1·60	1·50	0·82
Nicotine	11·2	9·28	34·00	—	—	—
Isoquinoline	13·9	11·3	0·01	0·20	0·40	0·20
Nornicotyrine	—	12·0	0·01	0·01	0·01	—
Myosmine	22·2	23·0	11·00	—	—	—
1,7-Diazaindene	76·3	61·8	—	—	0·01	0·01

* Yields (% by wt.) based on initial nicotine. † Gas–liquid chromatography, with pyridine as internal standard.

In order to study the pyrolysis factor only, we have used unpacked reactors and helium as inert atmosphere. The reactor exit streams were condensed in an air-cooled receiver

* Presented before the Thirteenth Tobacco Chemists Conference, Lexington, Kentucky, October, 1959.

[1] Bentley and Berry, "The Constituents of Tobacco Smoke: An Annotated Bibliography," Tobacco Manufacturers Standing Committee, London, 1959, pp. 19—24; also First Supplement thereto, 1960, pp. 10, 11.

[2] Cahours and Etard, *Compt. rend.*, 1880, **90**, 275; 1887, **105**, 1079; Oliveri, *Gazzetta*, 1895, **25**, 59; Woodward, Eisner, and Haines, *J. Amer. Chem. Soc.*, 1949, **66**, 911; Truhart and DeClerq, *Bull. Assoc. franç. Étude Cancer*, 1957, **41**, 426.

[3] Woodward, Badgett, and Williamson, *Ind. Eng. Chem.*, 1944, **36**, 540.

[4] Van Duuren, Bilbao, and Joseph, Amer. Chem. Soc., Meeting-in-Miniature, New York City, March, 1960.

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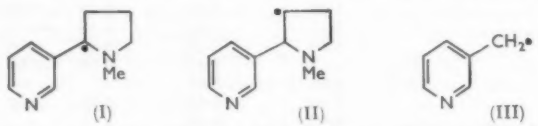
followed by a trap at −72°, and virtually all the volatile products were separated and characterized. The results are shown in the Table. Two compounds, isolated in small amounts were shown by their infrared spectra and reactivity towards cyanogen bromide and *p*-aminobenzoic acid [5] to be 3-substituted pyridine derivatives. Compound A is an unstable liquid colouring rapidly in air and possessing an ammoniacal odour; its ultraviolet spectrum is similar to that of metanicotine and the change of spectrum in alcoholic hydrogen chloride indicates marked basicity; but its infrared spectrum shows no similarity to that of metanicotine. Compound B occurs to a measurable extent only at 700° and is indicated by its acid shift of ultraviolet maxima to be less basic than compound A; it is a moderately stable liquid, discolouring only slowly in air.

By-products were not formed at <600°. The optical activity of nictotine before and after passage through the apparatus at 500° was little changed, indicating a high thermal stability.

In comparing these results with those of Woodward *et al.*[2], it is apparent that the pyrolytic environment is an important factor in determining the composition of the products: a vertical reactor: packed with quartz or activated alumina produced myosmine as the major product,[2] while our unpacked horizontal reactor gave almost equivalent quantities of myosmine and 3-vinylpyridine at 600°. The minor rôle of catalytic effects in the present work is further indicated by the low yield of 3-cyanopyridine, a major product when highly active catalysts are used.[3]

In our experiments no evidence was found for production of nornicotine, nicotyrine, *N*-methylmyosmine, nicotinamide, or nicotinic acid, all of which have been found when air was the carrier.

The nature of the compounds isolated, bond strengths, activation energies, and analogy with similar systems [6] led to a mechanism involving formation of the radical (I) from nicotine. The radical may react by elimination to form myosmine (3-2′-pyrrolinyl-



pyridine *) or rearrange to radical (II) which is free to form metanicotine by elimination. The subsequent reactions of myosmine yield nornicotyrine,† presumably by dehydrogenation. Whether this compound is cleaved to pyridine is problematical: the possibility of this is indicated by the rising yield of pyridine and the disappearance of myosmine in reactions at 760°.

Metanicotine, because of the yield and the facility with which it undergoes elimination,[9] must be an intermediate in the formation of 3-(buta-1,3-dienyl)pyridine. Isolation of the diene, quinoline, and isoquinoline supports the free-radical theories of Badger and Spotswood regarding the thermal synthesis of aromatic hydrocarbons like naphthalene

* Myosmine, first considered to be a Δ^2-pyrroline derivative, was believed by Späth *et al.*[7] to have a structure involving $\Delta^1 \longleftrightarrow \Delta^2$-pyrroline tautomerism. Eddy *et al.*,[8] finding no N–H bond at 3300 cm.$^{-1}$ in the infrared spectrum, favoured the pure 1-pyrrolinyl structure. Their work is supported by our studies which show a strong C=N bond stretching frequency at 1626 cm.$^{-1}$ and the complete lack of a trisubstituted ethylene band in the 840—790 cm.$^{-1}$ region.

† The formation of nornicotyrine from myosmine suggests that at high temperatures the tautomeric equilibrium is shifted towards the Δ^2-isomer. An alternative, less satisfactory, interpretation is that the Δ^1-isomer is dehydrogenated to form a transient pyrrolenine which immediately assumes the structure of nornicotyrine.

[5] Koenig, *J. prakt. Chem.*, 1904, **69**, 105.
[6] Roberts and Szwarc, *J. Chem. Phys.*, 1948, **16**, 981; Szwarc, *ibid.*, 1949, **17**, 431; Leigh and Szwarc, *ibid.*, 1952, **20**, 403, 844.
[7] Spath and Mamoli, *Ber.*, 1936, **69**, 757; Spath, Wenusch, and Zajic, *ibid.*, p. 393.
[8] Eddy and Eisner, *Analyt. Chem.*, 1954, **26**, 1428.
[9] Pinner, *Ber.*, 1914, **27**, 2866.

from 1-phenylbutadiene.[10] Precedent for the thermal synthesis of such heterocyclic systems exists in the pyrolysis of anabasine to 5-methylisoquinoline.[11]

The formation of 3-vinylpyridine in relatively large quantities at lower temperatures is evidence that under these conditions the primary reaction of 3-(buta-1,3-dienyl)pyridine is scission at the carbon–carbon single bond of the side chain rather than the alternate single bond joining the chain with the ring. This is in marked contrast to the pyrolysis of 1-phenylbutadiene where the analogous chain-scission is considered unimportant in the overall mechanism. The decrease in 3-vinylpyridine yield and the increase in that of pyridine with rise in temperature indicates either a change in the mechanism to favour cleavage adjacent to the ring or cleavage of 3-vinylpyridine. In addition to being a possible source of pyridine, 3-vinylpyridine is the most attractive source of 3-ethylpyridine and 3-picoline. These compounds would most logically arise by reduction, formation of radical (III) by disproportionation, and hydrogen abstraction to form 3-picoline.

While it is legitimate to discuss these products of pyrolysis in terms of free-radical reactions, it is possible to account for some of them by ion-controlled mechanisms. However, the occurrence of benzonitrile, 2- and 3-cyanopyridine, naphthalene, 1,7-diazaindene, quinoline, and isoquinoline can only be explained on the basis of free-radical reactions as studied by Badger and his co-workers [10,12] and of the types reviewed by Mapstone.[13] The isolation of 1,7-diazaindene is of particular interest as it allows the possibility of thermally initiated cyclization involving a three-atom rather than a four-atom side chain as in formation of quinoline, isoquinoline, and naphthalene.

Experimental

Nicotine.—The nicotine used in these studies was of reagent grade, fractionally distilled just before use; it had b. p. 240—242°/722 mm., $[\alpha]_D^{20}$ −161° 35′ (lit., $[\alpha]_D^{20}$ −166° 39′). Analysis by gas–liquid chromatography demonstrated no impurities.

Pyrolyses.—Nicotine (50 g.) was vapourized by flash-distillation (0·1 g./min.) at 280° into a helium stream (0·05 cu. ft./hr.) and passed through a 2·2 × 30 cm." Vycor " silica tube mounted in a horizontal electric combustion furnace controlled by a variable transformer. The apparatus was purged with helium (1 cu. ft./hr. for 10 min.) before use. The tube was fitted with ancillary heaters at the entrance and exit to prevent condensation and was wrapped with asbestos tape at the furnace junctions. Temperatures were controlled by a platinum/platinum–rhodium thermocouple inserted into a centre well in the reaction tube. Gradient measurements showed that uniform temperatures were maintained throughout a 150 c.c. volume of the tube. The outlet was fitted to an air-cooled receiver followed by a trap cooled in carbon dioxide–propan-2-ol. For results see the Table. Nicotine pyrolysed at 500° was quantitatively recovered, with $[\alpha]_D^{20}$ −151° 49′.

Gas–Liquid Chromatography of Products.—This was performed with a Wilkins " Aerograph " instrument. Operating parameters were: 200 mA filament current (hot-wire thermal conductivity cell), column temperature 200°; helium flow 0·06 cu. ft./hr. The columns were 0·25 in. × 8 ft. packed with 30—60 mesh C-22 acid-washed firebrick containing a 30% loading of " Carbowax 20 M " or " Ucon " (substituted polyethylene glycol). For completeness of separation the " Carbowax " columns were preferred. Quantitative measurements were made either by standard solutions for reference or by the peak-area technique.[14]

For preparative work the volatile part of the total product was removed by fractional distillation at atmospheric pressure and then subjected to gas–liquid chromatography through a 0·50 in. × 5 ft. " Ucon " column. The fractions were collected by direct condensation in m. p. capillaries. The majority of products were identified by the m. p.s of their picrates [15] and

[10] Badger and Spotswood, *J.*, 1959, 1635.
[11] Dubinin and Chelintsev, *J. Gen. Chem.* (*U.S.S.R.*), 1946, **16**, 105.
[12] Badger, Buttery, Kimber, Lewis, Moritz, and Napier, *J.*, 1958, 2449; Badger and Kimber, *J.*, 1958, 2453, 2455; 1960, 266, 2746; Badger and Buttery, *J.*, 1958, 2458, 2463.
[13] Mapstone, *Proc. Roy. Soc. New South Wales*, 1948, **82**, 96.
[14] Phillips, " Gas Chromatography," Butterworths, London, 1956, p. 63.
[15] Cheronis and Entrikin, " Semimicro Qualitative Organic Analysis," T. Y. Crowell Company, New York, 1947, p. 315.

mixed m. p.s, ultraviolet spectra (Beckman, model DK-2, ratio recording spectrophotometer, MeOH solutions), and infrared spectra (Beckman model IR-5 and Perkin–Elmer model 221 infrared spectrophotometers). Ancillary details are as follows.

Pyridine: picrate, twice crystallized from 95% ethanol, m. p. and mixed m. p. 167°, ultraviolet and infrared spectra.

3-*Picoline*: picrate, twice crystallized from 95% ethanol, m. p. and mixed m. p. 150°, ultraviolet and infrared spectra.

3-*Ethylpyridine*: picrate, m. p. 126°, once crystallized from 95% ethanol. The infrared spectrum was in agreement with that in the literature.[16]

Metanicotine: monopicrate, crystallized from 95% ethanol, m. p. 161° (Found: N, 17·9. Calc. for $C_{16}H_{17}N_5O_7$: N, 17·9%).

3-*Vinylpyridine*: picrate, crystallized from 95% ethanol, m. p. and mixed m. p. 143—144°, infrared and ultraviolet spectra.

3-(*Buta*-1,3-*dienyl*)*pyridine*: picrate, twice crystallized from 95% ethanol, m. p. 153—154° (lit.,[9] 151°) (Found: N, 15·6. Calc. for $C_{15}H_{13}N_4O_7$: N, 15·5%), $\lambda_{max.}$ 231 mμ, infl. 265 mμ; in alcoholic hydrogen chloride the maxima shifted to 259 mμ, and the inflection disappeared; infrared (KBr pellet) maxima at 3012, 2941, 2857, 1675, 1653, 1575, 1563, 1473, 1439, 1412, 1204, 962, 825, 770, and 706 cm.$^{-1}$.

3-*Cyanopyridine*: This compound crystallized in the capillary on emerging from the chromatograph. Identified by infrared and ultraviolet spectra, m. p. and mixed m. p. 49—50° after crystallization from hexane.

Naphthalene: crystallized in the capillary tube during collection, m. p. and mixed m. p. 79—80°.

2-*Cyanopyridine*: identified by retention time, ultraviolet and infrared spectra.

Quinoline: picrate, crystallized from 95% ethanol, m. p. and mixed m. p. 201—203°.

Isoquinoline: infrared and ultraviolet spectra.

Nornicotyrine: ultraviolet and infrared spectra and picrate, m. p. 198—200°, thrice crystallized from methanol (Found: N, 18·6. Calc. for $C_{15}H_{11}N_5O_7$: N, 18·8%).

Myosmine: ultraviolet and infrared spectra and picrate, m. p. 185° (Woodward *et al.*[2] give 183—184°) after crystallization from 95% ethanol.

Benzonitrile: the gross product from the 900° reaction was fractionated (0·5 mm.) through a 1·0 × 32·0 cm. column packed with glass helices. The fraction distilling at 50—80° was collected, dissolved in ether, and extracted with 6N-sulphuric acid. After evaporation, the residue was hydrolysed by refluxing 10% aqueous sodium hydroxide until no further ammonia evolved. Acidification of the solution gave benzoic acid, m. p. 120—121° after two crystallizations from water.

1,7-*Diazaindene*: crystallized in the capillary during collection, m. p. and mixed m. p. 105—106° after crystallization from hexane; picrate, m. p. 236—237° (from methanol) (Found: C, 45·0; H, 2·6; N, 20·2. Calc. for $C_{13}H_9N_5O_7$: C, 44·7; H, 2·7; N, 19·9%).

Compound "A": $\lambda_{max.}$ 246 mμ infl., 299 mμ; in alcoholic hydrochloric acid $\lambda_{max.}$ 224, 257, and (infl.) 298 mμ. $\nu_{max.}$ (in CCl_4) 3017, 2941, 2857, 1660, 1634, 1575, 1563, 1471, 1408, 1022, 915, 825, 792, 705, and 675 cm.$^{-1}$. Chromatography (ascending) on Whatman No. 1 paper with t-pentyl alcohol–0·2M-sodium acetate (1 : 1) gave R_F 0·25. A yellow Koenigs reaction product resulted with cyanogen bromide and *p*-aminobenzoic acid.

Compound "B": $\lambda_{max.}$ 222 and 287 mμ; in alcoholic hydrogen chloride $\lambda_{max.}$ 225 and 292 mμ; $\nu_{max.}$ (KBr pellet) 3049, 2924, 2222, 1724, 1590, 1565, 1511, 1433, 1404, 1434, 1308, 1295, 1241, 1206, 1081, 893, 793, 769, and 717 cm.$^{-1}$. Chromatography as above gave R_F 0·23. A yellow Koenigs reaction product was found.

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[16] Shindo and Ikekawa, *Pharm. Bull.* (*Japan*), 1957, **4**, 192.

474. *Chemical Applications of Nuclear Quadrupole Resonance. Part IV.*[1] *The Transmission of the Electronic Effect of Various Substituents by a Phosphorus Atom.*

By E. A. C. Lucken and M. A. Whitehead.

The ^{35}Cl nuclear quadrupole resonance frequencies of a number of derivatives of phosphoryl chloride and phosphorus trichloride are reported and are shown to be much less sensitive to the nature of the substituents than those of the corresponding carbon compounds. In contradiction to Jaffé and Freedman's ultraviolet spectroscopic observations,[2] substituents appear to be able to conjugate with the chlorine atom. Owing to the flexibility of the molecule, derivatives of phosphorus trichloride appear unlikely to yield easily interpretable quadrupole resonance frequencies.

Parts I—III of this series [1] have been concerned essentially with the effect of substituents on the ^{35}Cl-nuclear quadrupole resonance frequency of chlorine attached to a carbon atom. The nature of these effects and the mechanisms by which they are transmitted to the chlorine atom are, in this case, relatively well understood, much information being available from the large body of physicochemical experiment directed to the elucidation of the mechanism of organic reactions. When, however, electronic effects are transmitted through a phosphorus atom the situation is not so clear. Data derived from kinetic studies of substitution at a phosphorus atom are difficult to interpret unambiguously since the details of the mechanism of substitution have not yet been established; moreover, the rates of such reactions appear to be affected to a much greater extent by steric factors than are those of corresponding carbon compounds.[3] With these reservations, it appears, however, that the rates of hydrolysis of phosphonochloridates or related compounds are far less sensitive to the nature of the substituents than are those of the corresponding carbonyl compounds;[3] in addition conjugation appears to have far less importance. This is illustrated by the rate-constants shown in Table 1.[3]

Table 1. *Relative reactivities of phosphoryl and carbonyl compounds (data from ref. 5).*

Phosphoryl compounds	Relative rate	Carbonyl compounds	Relative rate
$(Et)_2POCl$ MeO·EtPOCl	15 : 1	Me·COCl EtO·COCl	10^4 : 1
Me_2POCl PhMePOCl	1·3 : 1	Me·COCl Ph·COCl	10^3 : 1

The apparent absence of conjugative effects has also been demonstrated by the ultraviolet [2] and infrared spectra [4] of phosphonic acids and their derivatives.

In the hope of obtaining further evidence the ^{35}Cl-nuclear quadrupole resonance frequencies of a number of derivatives of phosphorus oxychloride and phosphorus trichloride have been measured.

Experimental.—^{35}Cl-Nuclear quadrupole resonances were detected by using an externally quenched super-regenerative spectrometer based on that of Dean.[5] Frequencies were measured with a war-surplus frequency-meter of type BC 221 and are shown in Table 2. The compounds were supplied either by Dr. R. F. Hudson of this College or by Dr. Childs of Albright & Wilson Ltd. whose assistance is gratefully acknowledged. The main experimental difficulty lay in the purification of these highly reactive compounds and their subsequent crystallisation at 77° K. For almost all the compounds which did crystallise, very slow cooling was essential, and often crystallisation occurred only after numerous fruitless attempts. Often owing to the

[1] Parts I—III, *J.*, 1958, 2653; *J.*, 1959, 426, 2954.
[2] Jaffé and Freedman, *J. Amer. Chem. Soc.*, 1952, **74**, 1069.
[3] Hudson and Keay, *J.*, 1960, 1859.
[4] Bell, Heisler, Tannenbaum, and Goldenson, *J. Amer. Chem. Soc.*, 1954, **76**, 5185.
[5] Dean, Thesis, Harvard University, 1952.

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formation of glasses, experiments with the following substances failed: 2-methylprop-1-enyl- and 2-chloroethyl-phosphonic dichloride; dimethyl- and diphenyl-phosphinyl chloride; diethyl, dibutyl, and diphenyl phosphorochloridate; methyl methylphosphonochloridate;

TABLE 2. ^{35}Cl *nuclear quadrupole resonance frequencies in megacycles per second at 77° K.*

Compound	Frequency	Compound	Frequency
Phosphoryl chloride	28·989	Phenylphosphorodichloridate	27·7
	28·935	*NN*-Diethylphosphoramidic dichloride	27·034
Methylphosphonic dichloride	26·729		26·097
	26·426	*NN*-Diethyl-*P*-methylphosphon-	
Ethylphosphonic dichloride	26·332	amidic chloride	27·695
	26·194	Et methylphosphonochloridate	26·744
Chloromethylphosphonic dichloride ...	35·050		26·445
	26·872	Phosphorus trichloride	26·208
	26·172		26·104
Phenylphosphonic dichloride.....	25·357	Methylphosphonous dichloride	26·081
Me phosphorodichloridate	27·468	Phenylphosphonous dichloride.....	26·557
	27·099		

ethyl ethyl- and trichloromethyl-phosphonochloridate; ethylphosphonous dichloride; diphenylphosphinous chloride; ethyl phosphorodichloridite; and diethyl phosphorochloridite.

Spectra were measured as capillary films on a Grubb–Parsons recording double-beam grating spectrophotometer. The wavelengths of the P–O stretching frequencies were 7·96, 8·01, and 7·91 microns respectively.

Discussion.—Derivatives of phosphoryl chloride. In Table 3 the values of the nuclear quadrupole resonance frequencies of a number of monosubstituted phosphoryl chlorides are compared with the frequencies of the corresponding carboxylic acid chlorides, chloromethanes, and sulphonyl chlorides. Although the effects of the substituents are similar in the four series, the frequency shifts for the phosphorus derivatives are much less than for the others, in qualitative agreement with the kinetic data in Table 1. The reduced ability of phosphorus to transmit electronic effects is in accord with its greater polarisability; the opposite phenomenon is observed when inductive effects are transmitted through an oxygen atom,[6] as is illustrated in Table 4.

TABLE 3. *Comparison of* ^{35}Cl *nuclear quadrupole resonance frequencies of phosphoryl compounds with those of corresponding carbon and sulphur compounds.*

R	R·POCl$_2$	R·COCl	R·CH$_2$Cl	R·SO$_2$Cl	R	R·POCl$_2$	R·COCl	R·CH$_2$Cl	R·SO$_2$Cl
Cl	28·962	35·905[a]	35·991[d]	37·717[d]	Ph	25·357	29·93[a]	33·627[d]	32·63[h]
Cl·CH$_2$ ...	27·022	30·437[a]	34·361[e]		MeO ...	27·283	33·858[e]	30·181[g]	
Me	26·577	29·5[b]	32·70[d]	32·519[h]	PhO ...	27·70	—		
Et	26·263	—	32·968[e]		Et$_2$N ...	26·566	—		

[a] Bray, *J. Chem. Phys.*, 1955, **23**, 703. [b] Estimated. [c] Cl·CO$_2$Et: Weatherly and Williams, *J. Chem. Phys.*, 1954, **22**, 958. [d] Livingstone, *J. Phys. Chem.*, 1953, **57**, 496. [e] *Idem*, *J. Chem. Phys.*, 1952, **20**, 1170. [f] Ref. 6. [g] Part III, ref. 1. [h] Bray and Esteva, *J. Chem. Phys.*, 1954, **22**, 570.

TABLE 4. ^{35}Cl *Nuclear quadrupole resonance frequencies at 77° K.*

$CH_2{\cdot}CH_2{\cdot}CH_2Cl$	32·97	$\Delta = 0{\cdot}07$	$CH_2{\cdot}O{\cdot}CH_2Cl$	30·01(Av)	$\Delta = 2{\cdot}47$
$Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Cl$ ...	33·04 (Av)		$Cl{\cdot}CH_2{\cdot}O{\cdot}CH_2Cl$.....	32·48	

It is generally accepted that the phosphorus–oxygen bond in phosphoryl compounds has at least partial d_π–p_π multiple-bond character, and it is relevant to consider in more detail the structure of phosphorus oxychloride. Assuming that the molecule is held together by a tetrahedral sp^3 σ-bond framework, consider the extreme form where the phosphorus–oxygen bond is co-ordinate, as in amine oxides. The vacant 3*d*-orbitals on the phosphorus atom can now (*a*) remove the negative charge on the oxygen atom by

[6] Hooper and Blay, *J. Chem. Phys.*, 1960, **33**, 334.

multiple-bond formation, and (*b*) overlap with the unshared-electron orbitals on the chlorine atoms. Of these two effects the former is evidently the more important.

The phosphorus oxychloride molecule has C_{3v} symmetry. Let the *z*-axis lie along the P–O bond and thus the two occupied *p*-orbitals on the oxygen atom lie in the *x*–*y* plane. The transformation properties of these two orbitals and of the five *d*-orbitals of phosphorus under the group C_{3v} and of the group $C_{\infty v}$ corresponding to the " local " symmetry of the bond are given in Table 5. This shows that the *p*–*x* and *p*–*y* orbitals can interact to form

TABLE 5. *Orbital transformation properties.*

	C_{3v}	$C_{\infty v}$		C_{3v}	$C_{\infty v}$
dz^2	a_1	a_1	(dxz, dyz)	e	e_1
$(dx^2 - y^2, dxy)$	e	e_2	(x, y)	e	e_1

a multiple bond with the pair *dxz*, *dyz*. The overlap is illustrated in Fig. 1 and the calculations of Craig *et al.*[7] have shown that the magnitude of the overlap integral is sufficiently great for efficient bond formation.

The phosphorus–oxygen bond is thus seen to have the characteristics of a triple bond since both pairs of orbitals are equally capable of overlap. The charge transfer to the phosphorus atom will, however, be far from complete and the oxygen atom probably retains a net negative charge.

FIG. 1. P–O d_π–p_π *overlap.*

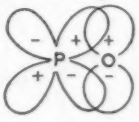
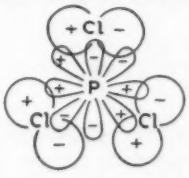


FIG. 2. P–Cl d_π–μ_π *overlap.*



Of the remaining *d*-orbitals the *dz*-orbital does not have the correct symmetry for d_π–p_π double-bonding. The dx^2–y^2 and *dxy* orbitals are, however, correctly oriented to overlap with the lone-pair orbitals on the chlorine atoms, as illustrated in Fig. 2. However, the *x*- and *y*-axes are not defined and the orientation has been arbitrarily chosen to illustrate the overlap. In fact, all three chlorine orbitals overlap equally with the degenerate pair of *d*-orbitals. The overlap will, however, be less than in the case of the phosphorus and oxygen orbitals because the chlorine atoms lie below the *x*–*y* plane containing the phosphorus atom and the phosphorus–chlorine bond is longer than the phosphorus–oxygen bond.

It can be concluded that in phosphoryl derivatives the substituents can conjugate weakly with the phosphorus atom and hence between themselves, but there is no direct conjugation with the phosphorus–oxygen bond. Observations of P–O stretching frequencies [4] are thus not relevant to the problem of the conjugating power of the phosphorus atom with other substituents. It should be noted, however, that the value of the overlap integral of the phosphorus *d*-orbitals with *p*-orbitals is very sensitive to the effective charge on the phosphorus atom and in this way pure inductive substituents could have an indirect conjugative effect.

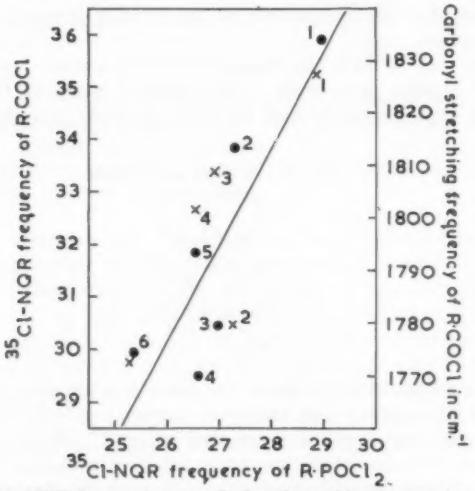
In Fig. 3 the quadrupole frequencies for the phosphoryl derivatives are plotted against quadrupole frequencies and the carbonyl infrared stretching frequencies of the corresponding carboxylic acid chlorides. In both cases there is a general correlation between the two seta of data. Because the R·COCl group is planar, the substituent R can conjugate with both the carbonyl group and the chlorine atom and any conjugative effect should show up in both nuclear quadrupole and infrared measurements, although probably not to

[7] Craig, McColl, Nyholm, Orgel, and Sutton, *J.*, 1954, 332.

the same extent. The correlation illustrated in Fig. 3 thus indicates that the nuclear quadrupole resonance frequencies of phosphoryl chlorides are also affected by conjugation, as predicted by the above theoretical discussion of the structure of these compounds.

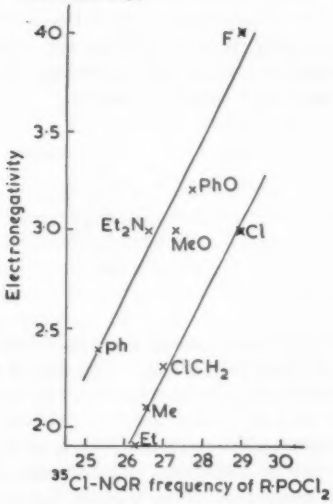
The carbonyl stretching frequencies of substituted ketones have been used as a measure of the effective electronegativity of the substituent,[8] but it was recognised that this electronegativity was a mixture of inductive and conjugative effects: In order to isolate the inductive electronegativity the P–O stretching frequencies of substituted phosphoryl compounds have been proposed since, as shown above, they should not be sensitive to

FIG. 3. *Comparison of* ^{35}Cl *nuclear quadruple stretching frequencies of* R·$POCl_2$ *with the corresponding quadruple frequencies and carbonyl stretching frequencies of* R·COCl. *The scales have been chosen so that the spreads of infrared and quadrupole frequencies correspond.*



● NQR *frequencies.* × *Carbonyl stretching frequencies.*
1, Cl. 2, MeO. 3, Cl·CH. 4, Me. 5, Et_2N. 6, Ph.

FIG. 4. *Group electronegativities and* ^{35}Cl *nuclear quadrupole frequencies of* R·$POCl_2$. (*The frequency for* $POFCl_2$ *was taken from ref. e of Table* **3**; *the electronegativities of the methyl, ethyl, and chloromethyl groups were derived from infrared measurements taken in this laboratory*).



conjugation.[4] In Fig. 4 the effective group electronegativities derived in this way are plotted against the quadrupole resonance frequencies. It is seen that two approximately parallel lines can be drawn through the points; one corresponding to substituents which are unlikely to conjugate, such as methyl, and the other corresponding to potentially conjugating substituents, such as methoxy. This again shows that the quadrupole frequencies are sensitive to conjugation.

TABLE 6. *Calculated and observed frequency shifts for disubstituted derivatives of phosphoryl chloride.*

R·$POCl_2$	ΔR $\nu_{(POCl_3)} - \nu_{(R\cdot POCl_2)}$	RR′POCl	$\Delta R + \Delta R'$	ΔR observed
Me·$POCl_2$	2·412	EtO·P(Me)·OCl	3·9	2·39
EtO·$POCl_2$	1·49			
Et_2N·$POCl_2$	2·423	Et_2N·P(Me)·OCl	4·8	1·29

Although the frequencies of monosubstituted phosphorus oxychlorides are more or less in accord with expectation, the frequencies of the disubstituted derivatives are anomalous. This can be seen by reference to Table 6, the frequencies of the disubstituted

[8] Kagarise, *J. Amer. Chem. Soc.*, 1955, **77**, 1377.

compounds being much higher than would be expected if the shifts were additive. This phenomenon is also observed in the P=O stretching frequencies [4] and the ^{31}P-nuclear magnetic resonance shifts of phosphoryl derivatives, particularly those having alkoxy- or alkylamino-substituents.[9] It is difficult to give any convincing explanation of this phenomenon and it would be desirable to have further data.

Derivatives of phosphorus trichloride.—Table 1 shows that only two derivatives of phosphorus trichloride gave quadrupole resonances and it is therefore impossible to build a comprehensive theory of the resonance frequencies of these compounds. Consideration of the results available indicates, however, that this is not likely to be profitable. In Table 7 the frequencies of the compounds measured are compared with those of corresponding carbon compounds and not only are the resonance frequencies very insensitive to the nature of the substituent but what effect there is lies in the opposite direction. This is almost certainly due to the fact that the bond angle in the pyramidal phosphorus trichloride molecule will be easily altered by substituents. This will alter the effective electronegativity of the phosphorus atom by changing the hybridisation of the bonds in the sense that the flatter the molecule the greater the *s*-character of the bonds and the greater the electronegativity of the phosphorus atom. It is unlikely, therefore, that further results will show much coherence.

TABLE 7. *Comparison of* ^{35}Cl *nuclear quadrupole resonance frequencies of derivatives of phosphorus trichloride with those of corresponding carbon compounds.*

R	R·PCl$_3$	R·CCl$_3$	R·CH$_2$Cl	RCl
Cl	26·156	40·64	36·235	54·48
CH_3	26·081	37·938	32·704	34·029
Ph	26·557	38·702	33·627	34·622

Conclusion.—The present results appear unfortunately to have confused an already difficult situation. Although the reduced sensitivity of phosphorus compounds to substituent effects is confirmed, the probable existence of a conjugative effect on the quadrupole resonance frequencies appears to contradict the ultraviolet observations of Jaffé and Freedman.[2] In a later paper,[10] however, Jaffé interprets some further ultraviolet measurements as indicating slight conjugation between a phenyl substituent and a phosphorus atom and a small but finite conjugation between two phenyl substituents attached to the same phosphorus atom. The kinetic data in Table 1 are consistent with interpretation of conjugation as less important for phosphorus compounds than for carbon compounds, as predicted in the theoretical discussion above, and the quadrupole results are likewise not inconsistent with this. Further experiment will be necessary to resolve the apparent conflict between the ultraviolet measurements and the present results.

We thank Dr. R. F. Hudson and Professor M. J. S. Dewar for their interest and helpful discussion, and the Central Research Fund of the University of London for a grant for apparatus. One of us (M. A. Whitehead) thanks the University of London for the award of the Arthur Jubber studentship for 1957—1958.

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[9] Muller, Lauterbur, and Goldenson, *J. Amer. Chem. Soc.*, 1956, **78**, 3557.
[10] Jaffé, *J. Chem. Phys.*, 1954, **22**, 1430.

475. *The Solubility of Plutonium Trifluoride, Plutonium Tetrafluoride, and Plutonium*(IV) *Oxalate in Nitric Acid Mixtures.*

By C. J. Mandleberg, K. E. Francis, and (in part) R. Smith.

The solubility of plutonium trifluoride has been measured in mixtures of nitric and hydrofluoric acids of various molarities and that of the tetrafluoride in nitric acid. The effect of fluoride ion on the solubility is discussed and an attempt made to estimate the solubility product of each compound. This is difficult because information about the activity coefficients of the species concerned is lacking. However, on the basis of the available data the solubility products appear to be trifluoride $2{\cdot}5 \times 10^{-16}$ and tetrafluoride 6×10^{-20}.

The solubility of plutonium(IV) oxalate has been determined in mixtures of nitric acid up to 3·52M and oxalic acid up to 0·6M. The minimum solubility occurs in 1M-nitric acid–0·01M-oxalic acid, but there is evidence that after 2—3 weeks' equilibration in this mixture an abnormal effect leads to anomalous solubilities.

Solutions of plutonium(IV) nitrate in nitric acid are commonly used as stock solutions of plutonium. For analytical or preparative purposes it is often convenient to precipitate from such a solution either the tri- or the tetra-fluoride or plutonium(IV) oxalate. In order to carry out such precipitations as completely as possible, it is essential to know the solubility of the required species at different concentrations of nitric acid and of hydrofluoric and oxalic acids, respectively. Such solubilities have been measured, and a number of points of interest have arisen in the course of this work.

Plutonium Trifluoride.—The effect of hydrofluoric acid upon the solubility of plutonium trifluoride in nitric acid was determined in two ways: (i) By adding hydrofluoric acid to solutions of the trifluoride in nitric acid of known molarities, determining the total hydrogen-ion concentration, agitating the precipitate and supernatant liquid, determining the concentration of plutonium in the latter, and calculating the concentration of fluoride ion. (ii) By agitating excess of solid trifluoride with mixtures of nitric and hydrofluoric acids of predetermined molarities, and determining the concentration of plutonium in the supernatant liquid.

The solubility of *plutonium trifluoride* in nitric acid is so drastically lowered by the addition of fluoride ion, and the amount of trifluoride precipitated is so large, that the difference between the two titration values does not represent the true molarity of hydrogen fluoride after precipitation. The true molarity was calculated to give the values shown in Table 1*a*.

In principle the concentration of nitric acid must be increased by an equivalent amount, but even where the correction to the concentration of hydrofluoric acid is appreciable the equivalent correction to the concentration of nitric acid is not significant.

From the solubilities of plutonium trifluoride in nitric acid free from hydrofluoric acid the solubility product of the trifluoride, $[Pu][F]^3 = C_{PuF_3}$, can be obtained. The concentration of fluoride ion in the presence of excess of nitric acid must itself be calculated because the concentration of free fluoride ion in the presence of hydrogen ion is so small. Sidgwick [1] quotes $K_1 = [H][F]/[HF] = 7{\cdot}2 \times 10^{-4}$ (which involves, for example, only 1% of free fluoride ion in concentrated hydrofluoric acid), and records the second equilibrium constant $K_2 = [F_2H]/[F][HF] = 5{\cdot}5$.

In the evaluation of K_1, the concentration of hydrogen ion must be known. The best values for the dissociation of nitric acid appear [2] to be 98% in M and 92% in 2M solution, and [H] has been calculated on this basis.

[1] Sidgwick, "Chemical Elements and their Compounds," Oxford, 1959, p. 1105 *et seq.*
[2] McKay, private communication.

TABLE 1. *Solubility of plutonium trifluoride in nitric acid–hydrofluoric acid (g./l. of* Pu *at* 25°). [(*a*) Corrected concentration of hydrofluoric acid (M); (*b*) solubility of plutonium(III) ion (g./l.).]

(*a*) *First method.*

HNO_3 (M)								
0·05	(*a*) 0·00	0·054	0·96	1·65	2·5	3·9	6·07	7·45
	(*b*) 0·157	0·080	0·067	0·049	0·038	0·039	0·041	0·044
0·16	(*a*) 0·00	0·52	1·00	1·68	3·34	4·94	6·84	7·94
	(*b*) 0·202	0·137	0·082	0·064	0·057	0·046	0·037	0·024
0·30	(*a*) 0·00	0·59	1·33	2·09				
	(*b*) 0·955	0·068	0·049	0·050				
0·61	(*a*) 0·00	0·57	1·074	2·01	3·07			
	(*b*) 1·710	0·233	0·074	0·058	0·070			
1·20	(*a*) 0·00	0·57	1·17	1·73	2·37	3·97	6·87	
	(*b*) 2·691	0·319	0·102	0·088	0·065	0·053	0·048	
2·40	(*a*) 0·00	0·35	0·65		2·31			
	(*b*) 4·589	0·141	0·097		0·064			

(*b*) *Second method*

1·13	(*a*) 0·3	0·8	1·25	1·65		
	(*b*) 0·084	0·047	0·040	0·014(?)		
2·25	(*a*) 0·03	0·7	1·15	1·55	3·00	4·35
	(*b*) 0·073	0·053	0·038	0·019	0·055	0·059

The solubility product of plutonium trifluoride is then given by the expression

$$C_{PuF_3} = \left[\frac{K_1\,[HF]}{f\,[HNO_3]}\right]^3 [Pu]$$

where $K_1 = 7{\cdot}2 \times 10^{-4}$ and f is a factor based on the dissociation of nitric acid.

TABLE 2. *Solubility product of plutonium trifluoride.*

$[HNO_3]$ (M) ...	0·054	0·16	0·30	0·61	1·20	2·40
C_{PuF_3}	$1{\cdot}18 \times 10^{-17}$	$1{\cdot}15 \times 10^{-16}$	$1{\cdot}08 \times 10^{-16}$	$1{\cdot}45 \times 10^{-16}$	$5{\cdot}95 \times 10^{-16}$	$4{\cdot}45 \times 10^{-16}$

At first sight this might be taken to show a slight upward trend in solubility product with increasing concentration of nitric acid. However, the acid concentration is derived by microtitration, and since calculation of the solubility product involves a third power of the concentration of hydrogen ion too much reliance should not be placed on the values at the lowest acidity. On the other hand, the calculation omits any consideration of the activity coefficients of the species involved, and the correction which they would introduce might increase the values of C_{PuF_3} much more (possibly by a power of ten) at lower acidities than at higher. Information for the precise application of this correction is not available but the evidence suggests that it would make the values of C_{PuF_3} more constant. The assumption has also been tacitly made that the concentration of free fluoride ion is negligible by comparison with that of hydrofluoric acid, and thus that the latter can be set equal to the concentration of dissolved fluoride. This cannot be true at acidities below about 0·1M, particularly as the total fluoride molarity is also low at this acidity. The best mean value of the solubility product can be taken as $C_{PuF_3} = 2{\cdot}5 \times 10^{-16}$.

The abrupt flattening of the solubility curves with increasing concentration of hydrofluoric acid does not necessarily indicate complexing of plutonium(III), being rather the behaviour to be expected from the small dissociation of the hydrofluoric acid itself. At concentrations of hydrofluoric acid above 2M, the addition of more acid does not appreciably affect the concentration of fluoride ion. The agreement between the results in Table 1*a* and Table 1*b* is as good as can be expected from the short time allowed for equilibration. The solubility of plutonium trifluoride in hydrofluoric acid–nitric acid mixtures, where the hydrofluoric acid molarity is greater than 2M, can be confidently stated to lie between 0·035 and 0·065 g. of Pu/l.

Plutonium Tetrafluoride.—The solubility of plutonium tetrafluoride was measured in nitric acid solutions only.

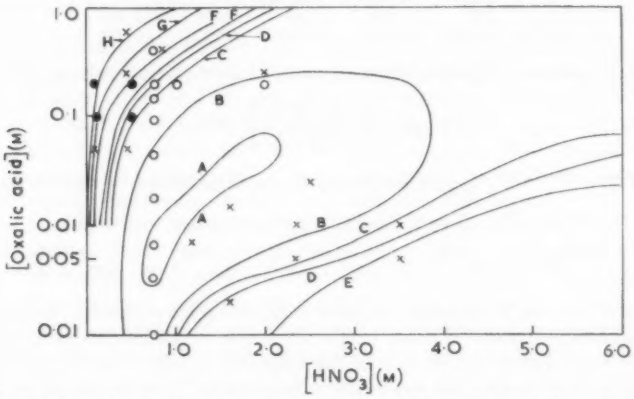
TABLE 3. *Solubility of plutonium tetrafluoride* (*g. of* Pu/*l.*).

$[HNO_3]$	Concn. Pu	Solubility product	$[HNO_3]$	Concn. Pu	Solubility product
0·00	0·060	$(2·55 \times 10^{-16})$	0·74	2·90	$5·32 \times 10^{-20}$
0·015	0·088	$0·82 \times 10^{-20}$	1·00	4·19	$16·0 \times 10^{-20}$
0·15	0·460	$0·32 \times 10^{-20}$	1·59	5·8	$8·0 \times 10^{-20}$
0·30	0·820	$0·36 \times 10^{-20}$	3·19	10·4	$23·0 \times 10^{-20}$
0·59	2·24	$7·31 \times 10^{-20}$			

The solubility product was calculated in a similar manner to that already described for the trifluoride. The only other published value for the solubility is *ca.* 0·1 g./l. in water (two values in hydrofluoric–nitric acids mixtures are also reported [3]).

There is good evidence of complex-formation in plutonium(IV) solutions in nitric acid, but there is little evidence of this in the solubility product of plutonium(IV) fluoride. This shows a change comparable with that of C_{PuF_3}, which was attributed to the absence of activity coefficients and the formal assumption that $[F'] = [HF]$, which does not hold at

Solubility of plutonium(IV) *oxalate in nitric acid–oxalic acid mixtures at* 26·5°. *Isosols join points of equal solubility* (*expressed in mg. of plutonium per litre*).



A, 10 mg./l. B, 20 mg./l. C, 40 mg./l. D, 60 mg./l. E, 80 mg./l. F, 100 mg./l. G, 130 mg./l. H, 200 mg./l.

×, This paper. ●, O'Conner (ref. 5). ○, Reas (ref. 4).

the lowest acidities. On the evidence, $6·0 \times 10^{-20}$ is probably the best value for the solubility product of the tetrafluoride.

Plutonium(IV) *Oxalate.*—There is good agreement between our results, American data,[4,5] and those of Kemp and Welch.[6] The last measured the solubility of plutonium(IV) oxalate by precipitation with oxalic acid and determination of the plutonium content of the supernatant liquor. They found that the concentration of plutonium in this liquor decreased during the first 100—500 hr., and then increased. Sometimes the rate of increase was rather rapid. They attributed the increase in solubility to some decomposition of the oxalate by the nitric acid. However, their figures for the solubilities near the minimum (*i.e.* after 100—500 hr.) agree well with those now reported (14—21 days' equilibration) for comparable concentrations of acid. We found a similar solubility minimum on only three occasions, but unfortunately the solutions concerned were discarded after 21 days and before Kemp and Welch's results were available to us.

It may be that oxidation progresses at a finite rate throughout equilibration, but since

[3] Meyer and Zoolner, CK. 1763.
[4] Reas, " The Transuranium Elements," NNES, Vol. XIVb, paper 4.9, p. 423.
[5] O'Connor, CN. 1702.
[6] Kemp and Welch, U.K.A.E.A., C.1, report 69.

there is such good agreement between our results and the findings of Reas, of O'Connor, and of Kemp and Welch it seems unlikely that the acid concentrations were appreciably changed from their nominal values by such an oxidation during 3 weeks. If oxidation is the explanation of the occasional anomalies which we found, there would appear to be an induction period of at least 2—3 weeks. It seems reasonable to conclude that the solubility values in the Figure and Table 4 are reliable over the range of concentrations investigated, where the precipitation is completed in less than 10—14 days.

Experimental

Plutonium Trifluoride.—Method (i). Plutonium trifluoride was prepared by passing sulphur dioxide through a plutonium(IV) nitrate solution (8 g. of Pu/l.) for 15 min. and then adding hydrofluoric acid in slight excess to the plutonium(III) nitrate solution thus produced. The solution was centrifuged and the precipitate well washed with distilled water to remove excess of fluoride ion.

Various concentrations were prepared of nitric acid containing 10 g./l. of hydroxylamine to prevent the oxidation of plutonium(III) by atmospheric oxygen. The acid concentration was determined by titration with standard sodium carbonate.

To each solution (in lusteroid tubes) an excess of solid plutonium trifluoride was added, and the mixtures were agitated in a thermostat at 25° for 15—18 hr. The tubes were then centrifuged, the liquid was removed, and the concentration of plutonium determined by counting the alpha activity of an aliquot portion in a Simpson chamber, the efficiency of which had been checked with a standard source counted in a Ward chamber of known geometry. The maximum counting error was probably $\pm 1\%$.

To the supernatant liquid from each determination was added one drop of 40% aqueous hydrofluoric acid, which caused further precipitation of fluoride; the total acidity of each solution was determined by titration, a calibrated Rehburg microburette being used. The solution and precipitate were then agitated for 15—18 hr. at 25° and the plutonium concentration in the supernatant liquid determined as before, care being taken that (*a*) there was always an excess of solid trifluoride during equilibration, and (*b*) the solid was violet and the solution blue. When, as in a few determinations, the excess of solid or the solution appeared greenish, the results were discarded since oxidation to plutonium(IV) had take place.

The procedure was repeated in each case, after more hydrofluoric acid solution had been added.

Method (ii). Two solutions (1·15M and 2·25M) of nitric acid each containing 10 g./l. of hydroxylamine hydrochloride were prepared and standardised. To portions of each, different amounts of 40% aqueous hydrofluoric acid were added, and the total acidity determined by titration. To each solution was added an excess of solid plutonium trifluoride, and the mixtures were agitated at 25° for 15—18 hr. They were then centrifuged, and the concentrations of plutonium in the supernatant liquid determined.

Plutonium Tetrafluoride.—Purest available plutonium(IV) nitrate dissolved in 3M-nitric acid was precipitated with a 40% aqueous solution of hydrofluoric acid added dropwise. The supernatant liquid was removed after centrifugation, and the precipitate was washed repeatedly to remove all traces of hydrofluoric acid. Nitric acid solutions were accurately standardised against sodium carbonate solutions. Portions of the washed plutonium tetrafluoride, together with a few ml. of the standardised nitric acid, were placed in stoppered tubes. A rotary stirrer holding such tubes was designed, and the whole immersed in a thermostat bath at 26·8°. The solubility at each molarity of nitric acid was determined in duplicate, and the concentration of plutonium was found by withdrawing an aliquot portion, diluting it accurately 100—1000 fold as necessary, and preparing from an aliquot portion a source which was counted in a Simpson chamber whose geometry was determined in each case by means of a source accurately standardised in a Ward chamber. Equilibrium was assumed to be attained when two samples withdrawn at intervals of 48 hr. had the same concentration to within 1%, and when the concentration in the two duplicate samples also agreed within 1%.

Plutonium(IV) *Oxalate.*—This was precipitated by adding a small excess of oxalic acid crystals to plutonium(IV) nitrate in 6M-nitric acid. The precipitate was well washed to remove nitric and oxalic acids.

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Portions of this oxalate were continuously agitated with nitric acid–oxalic acid of known strengths in a thermostat at 27°. Equilibrium was achieved after agitation for 2—3 weeks. The solubility of the plutonium was then determined by pipetting portions of the supernatant liquid on to counting trays and measuring the alpha activity in a proportional counter. Each operation was carried out in duplicate and the values were accepted only when four determinations agreed within a few units per cent; these are shown in Table 4.

TABLE 4.

$[HNO_3]$ (M)	$[(COOH)_2]$ (M)	Solubility (g. of Pu/l.)	$[HNO_3]$ (M)	$[(COOH)_2]$ (M)	Solubility (g. of Pu/l.)	$[HNO_3]$ (M)	$[(COOH)_2]$ (M)	Solubility (g. of Pu/l.)
0·0	0·0	45·9	0·78	0·40	144	2·00	0·0	128
,,	0·05	334	1·00	0·0	122	,,	0·05	9·7
,,	0·25	242	,,	0·05	13·3	,,	0·25	15·1
0·1	0·0	26·6	,,	0·25	36·9	2·34	0·01	15·3
,,	0·5	132	,,	0·60	133	,,	0·005	24·9
0·5	0·0	69·0	1·18	0·0071	16·3	2·52	0·025	16·7
,,	0·05	26·6	1·61	0·002	65·8	3·52	0·005	92·1
,,	0·25	97·1	,,	0·015	15	,,	0·01	45·8
,,	0·60	361				,,	0·05	18
						,,	0·1	18·2
						,,	0·5	21·4

Solubility contours have been plotted in order to express these results on a two-dimensional graph. The Figure shows the concentration of nitric acid as abscissa on a linear scale, and that of oxalic acid as ordinate on a logarithmic scale. Smooth curves have been drawn to join points representing concentrations at which the solubility of plutonium is equal.

The authors are indebted to Mr. H. A. C. McKay for discussions concerning the plutonium fluorides, and to Professor P. L. Robinson for his assistance in drafting this paper.

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[*Received October 28th*, 1960.]

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476. *The Reaction of 2-Amino-2-deoxy-D-glucose Hydrochloride with Aqueous Ammonia.*

By MAHMOUD I. TAHA.

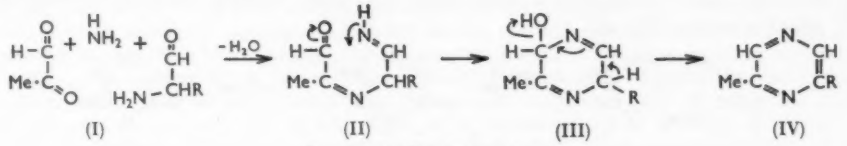
The products of the action of aqueous ammonia on 2-amino-2-deoxy-D-glucose hydrochloride at room temperature have been separated by chromatography on cellulose. They include 2-methyl-6-D-*arabo*-tetrahydroxybutyl-, 2-methyl-5-D-*arabo*-tetrahydroxybutyl-3-D-*erythro*-trihydroxypropyl-, and 2,5-bis-(D-*arabo*-tetrahydroxybutyl)-pyrazine.

SUGAR solutions containing ammonia develop a colour which changes from pale cream to dark brown,[1] a reaction attributed both to the alkaline reaction [2] of ammonia and to its effect as an amino-compound.[1,3] The alkaline action leads to rearrangement [4] and fragmentation,[5] while condensation of ammonia with the products yields nitrogen-containing heterocyclic compounds.[1] With non-amino-bases amino-sugars, *e.g.*, 2-amino-2-deoxy-D-glucose at room temperature, undergo deamination,[6] accompanied by epimerisation of the deaminated sugar, yielding D-glucose, D-fructose, and saccharinic acids. I

[1] Hough, Jones, and Richards, *J.*, 1952, 3854; 1953, 2005; 1954, 295; Ling and Nanji, *J. Soc. Chem. Ind.*, 1922, **41**, 151T.
[2] Whistler and Bemiller, *Adv. Carbohydrate Chem.*, 1958, **13**, 289; Wolfrom, Cavalieri, and Cavalieri, *J. Amer. Chem. Soc.*, 1947, **69**, 241.
[3] Ellis, *Adv. Carbohydrate Chem.*, 1959, **14**, 63.
[4] Lobry De Bruyn and Alberda Van Ekerstein, *Rec. Trav. chim.*, 1895, **14**, 150, 195; 1899, **18**, 147; and other papers.
[5] Nef, *Annalen*, 1907, **357**, 294; 1910, **376**, 1; 1913, **403**, 204; Schmidt, *Chem. Rev.*, 1935, **17**, 137.
[6] Tracey, *Biochem. J.*, 1952, **52**, 265.

have therefore, investigated the action of aqueous ammonia on 2-amino-2-deoxy-D-glucose.

2-Amino-2-deoxy-D-glucose hydrochloride and aqueous ammonia were allowed to react for six months at room temperature. The optical rotation of the mixture decreased to zero in seven days, after which the intensity of the brown colour prevented estimation of the rotation. Meanwhile the absorption at 2750 Å increased continuously. Paper chromatography revealed at least five components. Chromatography on a column of cellulose afforded five materials, one of them being unchanged 2-amino-2-deoxy-D-glucose. The second component was crystalline 2-methyl-6-D-*arabo*-tetrahydroxybutylpyrazine (IV) which had been obtained by Hough, Jones, and Richards [1] by a similar reaction of D-glucose with aqueous ammonia. It is probable that the pyrazine derivative (IV) is formed by condensation (I—IV) of *aldehydo*-2-amino-2-deoxy-D-glucose with ammonia and methylglyoxal. The glyoxal could arise from 2-amino-2-deoxy-D-glucose by fragmentation and transformation.

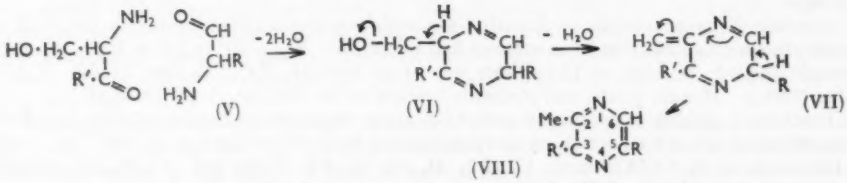


(I) (II) (III) (IV)

R = D-*arabo*-Tetrahydroxybutyl.

The alternative condensation product, 2-methyl-5-D-*arabo*-tetrahydroxybutylpyrazine was not isolated.

The third component was a crystalline non-reducing compound $C_{12}H_{20}N_2O_7$ (Y) containing one *C*-methyl group, giving a crystalline heptabenzoate, and containing a pyrazine nucleus [$\lambda_{max.}$ 2800 Å (ε 9420) in water]. Oxidation by periodate afforded two mol. of formaldehyde, indicating the presence of two carbon chains each ending with at least two hydroxyl groups on adjacent carbon atoms. One of the periodate products was isolated (in 9·7% yield) as the crystalline 2,4-dinitrophenylhydrazone $C_{10}H_{15}IN_6O_4$ (Z) containing no pyrazine nucleus (as indicated by the ultraviolet absorption) but one *C*-methyl group; the high melting point (192°) suggested that it was a hydriodide and indeed with aqueous ammonia it afforded a base $C_{10}H_{14}N_6O_4$. Since compound (Z) is derived from a pyrazine derivative, the two nitrogen atoms must be linked to adjacent carbon atoms and it is evident from the empirical formula that they can only be present as amino-groups. This gains some support from the fact that primary amino-groups were detected during the oxidation of compound (Y) by periodate. Compound (Z) is, therefore, probably 2,3-diaminobutanal 2,4-dinitrophenylhydrazone hydriodide. Its isolation shows that the pyrazine nucleus of its parent (Y) is destroyed by periodate, in conformity with the high uptake (8 mols.). It also shows that the methyl group of the parent compound (Y) is attached directly to the pyrazine ring, and that the carbon atom carrying the methyl group



(V) (VI) (VII) (VIII)

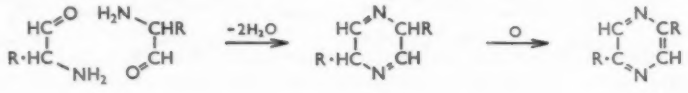
R = D-*arabo*-Tetrahydroxybutyl. R′ = D-*erythro*-Trihydroxypropyl.

is adjacent to one carrying one of the carbon chains (R in VIII). The second carbon chain, therefore, must be attached to the other side of the pyrazine ring.

It is evident that compound (Y) ($C_{12}H_{20}N_2O_7$) could be formed from two molecules

of 2-amino-2-deoxy-D-glucose ($C_6H_{13}NO_5$) by the loss of three molecules of water, *e.g.*, (V—VIII). This condensation would result in a molecule with six carbon atoms on either side of the plane of the nitrogen atoms which would allow a three-carbon chain on the side of the pyrazine nucleus carrying the methyl group, and a four-carbon chain on the other side of the nucleus. The four-carbon chain will necessarily be located at position 5. From all these considerations it is suggested that compound (Y) is 2-methyl-5-D-*arabo*-tetrahydroxybutyl-3-D-*erythro*trihydroxypropylpyrazine (VIII).

The fourth component was crystalline 2,5-bis-(D-*arabo*-tetrahydroxybutyl)pyrazine (XI) which was reported [7] to be formed in aqueous solutions of 2-amino-2-deoxy-D-glucose. It yielded a crystalline octa-acetate and octabenzoate and its ultraviolet absorption curve was similar to those of compounds (IV) and (VIII) [$\lambda_{max.}$ 2750 Å (ε 9410) in water]. On oxidation by potassium permanganate, compound (XI) yielded pyrazine-2,5-dicarboxylic acid; it consumed six mols. of periodate with the simultaneous liberation of four mols. of formic acid and two of formaldehyde. It is probably formed by condensation of two molecules of *aldehydo*-2-amino-2-deoxy-D-glucose, yielding the dihydro-compound (X) which is oxidised by air.



(IX) (X) (XI)

R = D-*arabo*-Tetrahydroxybutyl.

The fifth component was a dark brown amorphous substance which is under investigation.

Experimental

Paper chromatography was made on Whatman No. 1 filter paper, by the descending method with ethyl acetate–acetic acid–water (9 : 2 : 2 v/v) as mobile phase. The separated substances were detected with (*a*) a 4% solution of silver nitrate containing an excess of ammonia,[8] or (*b*) 0·1% ninhydrin in butan-1-ol. Solutions were evaporated under reduced pressure. Optical rotations refer to room temperature.

Reaction of 2-Amino-2-deoxy-D-glucose Hydrochloride with Aqueous Ammonia.—A mixture of 2-amino-2-deoxy-D-glucose hydrochloride (50 g.) and aqueous ammonia (500 ml.; *d* 0·88) was kept at room temperature. At intervals samples (1 ml.) were diluted ten-fold with distilled water, and their optical rotations estimated. Of the diluted solution 1 ml. was further diluted forty-fold before its absorption at 2750 Å was determined (Unicam S.P. 500). After 6 months, the remainder (*ca.* 98%) of the reaction mixture was concentrated to dryness to remove the excess of ammonia. The product was dissolved in water (200 ml.), deionised by Permutit " Deacidite H " (100 g.) and then Permutit ZeoKarb 225 (100 g.), and concentrated to a brown syrup (*ca.* 36 g.) which, when examined on paper chromatograms with spray (*a*), was observed to contain at least four products (R_F 0·705, 0·673, 0·46, 0·0). The syrup was fractionated on a cellulose column with butan-1-ol–water (10 : 1 v/v) as mobile phase. Three fractions were obtained.

Fraction 1 gave crystals of 2-methyl-6-D-*arabo*-tetrahydroxybutylpyrazine (*ca.* 0·63 g.) which after recrystallisation from ethanol had m. p. 170°, $[\alpha]_D$ −70° (*c* 1·0 in H_2O), R_F 0·705 (Found: C, 50·3; H, 6·65; N, 13·1; *C*-Me, 6·3. Calc. for $C_9H_{14}N_2O_4$: C, 50·5; H, 6·5; N, 13·1; *C*-Me, 7·0%). Hough, Jones, and Richards [1] record m. p. 170°, $[\alpha]_D$ −74° (in H_2O).

Fraction 2 yielded crystalline 2-*methyl*-5-D-arabo-*tetrahydroxybutyl*-3-D-erythro-*trihydroxypropylpyrazine* (*ca.* 2·2 g.) which on recrystallisation from ethanol had m. p. 152°, $[\alpha]_D$ −100° (*c* 1·32 in H_2O), R_F 0·673 (Found: C, 47·3; H, 6·7; N, 9·3; *C*-Me, 4·2. $C_{12}H_{20}N_2O_7$ requires C, 47·3; H, 6·6; N, 9·2; *C*-Me, 4·9%).

Fraction 3 afforded 2,5-bis-(D-*arabo*-tetrahydroxybutyl)pyrazine as crystals (*ca.* 1·8 g.), m. p. 235° (from ethanol), $[\alpha]_D$ −76° (*c* 1·4 in H_2O), R_F 0·46 (Found: C, 44·85; H, 6·35; N, 9·0.

[7] Stolte, *Beitr. Chem. Physiol.*, 1908, **11**, 19.
[8] Partridge, *Biochem. J.*, 1948, **42**, 238.

Calc. for $C_{12}H_{20}N_2O_8$: C, 45·0; H, 6·25; N, 8·75%). Stolte [7] recorded m. p. 232·5°, $[\alpha]_D$ −71° (in H_2O).

A fourth fraction was obtained by washing off the brown material, which had been stationary on top of the cellulose column, with water. On concentration the washings yielded a dark brown amorphous solid (*ca.* 18·6 g.). It is under investigation.

*2-Methyl-6-*D*-arabo-tetra-acetoxybutylpyrazine.*—A mixture of 2-methyl-6-D-*arabo*-tetrahydroxybutylpyrazine (fraction 1) (22 mg.), dry pyridine (0·5 ml.), and acetic anhydride (0·5 ml.) was set aside at room temperature for 24 hr. and then poured into ice water (*ca.* 10 ml.). The *acetate* was extracted with chloroform (3 × 2 ml.), and the combined extracts were washed successively with 2N-hydrochloric acid (2 × 2 ml.), 2N-sodium hydrogen carbonate (2 × 2 ml.), and water, and dried (Na_2SO_4). Subsequent concentration gave a colourless syrup (44 mg.) (Found: C, 53·5; H, 5·9; N, 7·2; Ac, 41·8. $C_{17}H_{22}N_2O_8$ requires C, 53·4; H, 5·8; N, 7·3; Ac, 44·7%).

*2-Methyl-5-*D*-arabo-tetrabenzoyloxybutyl-3-*D*-erythro-tribenzoyloxypropylpyrazine.*—2-Methyl-5-D-*arabo*-tetrahydroxybutyl-3-D-*erythro*-trihydroxypropylpyrazine (fraction 2) (0·1 g.), dry pyridine (2 ml.), and benzoyl chloride (2 ml.) was left at room temperature overnight and poured into ice-cold saturated sodium hydrogen carbonate solution (*ca.* 20 ml.). The oily product which separated was dissolved in chloroform (10 ml.), washed successively with 2N-hydrochloric acid (2 × 10 ml.), sodium hydrogen carbonate (2 × 10 ml.), and water, and dried (Na_2SO_4). On concentration the chloroform solution afforded the *heptabenzoate* as needles (0·214 g.) which after recrystallisation from acetone–light petroleum (b. p. 40—60°) had m. p. 163° (Found: C, 71·0; H, 4·9; N, 2·8. $C_{61}H_{48}N_2O_{14}$ requires C, 71·0; H, 4·65; N, 2·8%).

2,3-Diaminobutanal 2,4-Dinitrophenylhydrazone Hydriodide.—Sodium metaperiodate (3 g.) in water (50 ml.) was added with stirring to 2-methyl-5-D-*arabo*-tetrahydroxybutyl-3-D-*erythro*-trihydroxypropylpyrazine (fraction 2) (0·5 g.). After 3 hr. the product was extracted with chloroform (10 ml.), washed with 1% sodium thiosulphate solution (2 × 10 ml.) and then with water, dried, and concentrated. The syrupy product was heated with 2,4-dinitrophenylhydrazine (0·1 g.) in ethanol (10 ml.) under reflux for 5 min., after which the mixture was cooled and concentrated hydrochloric acid (0·5 ml.) was added. The *dinitrophenylhydrazone* (65 mg.) formed needles (from ethanol), m. p. 192° (Found: C, 29·1; H, 3·8; I, 29·6; N, 20·4; *C*-Me, 2·5. $C_{10}H_{15}IN_6O_4$ requires C, 29·3; H, 3·7; I, 31·0; N, 20·5; *C*-Me, 3·7%).

2,3-Diaminobutanal 2,4-dinitrophenylhydrazone (*ca.* 5 mg.) was obtained from the hydriodide (23 mg.) by recrystallisation from aqueous ethanol (5 ml.) containing ammonia solution (1 drop; *d* 0·88). It had m. p. 135° (Found: C, 42·9; H, 4·9. $C_{10}H_{14}N_6O_4$ requires C, 42·55; H, 5·0%).

2,5-Bis-(D-arabo-*tetra-acetoxybutyl*)*pyrazine.*—The crystalline *octa-acetate* (44 mg.) was obtained from 2,5-bis-(D-*arabo*-tetrahydroxybutyl)pyrazine (fraction 3) (40 mg.) as above. On recrystallisation from acetone–light petroleum (b. p. 40—60°) it had m. p. 175° (Found: C, 51·2; H, 6·3; N, 4·5; Ac, 54·9. $C_{28}H_{36}N_2O_{16}$ requires C, 51·2; H, 6·2; N, 4·3; Ac, 52·5%).

The *octabenzoate* (24 mg.) was also obtained from the pyrazine derivative (fraction 3) (15 mg.) as above. It afforded needles (from ethanol), m. p. 120° (Found: C, 72·6; H, 4·7; N, 2·3. $C_{68}H_{52}N_2O_{16}$ requires C, 72·5; H, 4·5; N, 2·4%).

Pyrazine-2,5-dicarboxylic Acid.—2,5-Bis-(D-*arabo*-tetrahydroxybutyl)pyrazine (*ca.* 0·5 g.) in 5N-sulphuric acid (10 ml.) was titrated dropwise with saturated potassium permanganate solution until the pink colour persisted. The product was extracted with chloroform (3 × 5 ml.), washed with water, and dried (Na_2SO_4). Concentration of the chloroform extract afforded crystalline pyrazine-2,5-dicarboxylic acid (85 mg.). On purification by sublimation [9] this had m. p. 253° (sealed tube). It gave a bluish-violet colour with ferrous sulphate solution (Found: C, 42·8; H, 2·4; N, 17·0. Calc. for $C_6H_4N_2O_4$: C, 42·9; H, 2·4; N, 16·7%). Stoehr [9] records m. p. 255—256°.

Periodate Oxidations.—In each case, a mixture of *ca.* 0·3N-sodium metaperiodate (10 ml.) and the compound (*ca.* 100 mg., accurately weighed) was made up to 100 ml. with distilled water and stored in the dark. A control containing none of the compound was handled concurrently. At intervals, the periodate uptake was estimated by transferring samples (5 ml.) from the oxidation mixture and from the control into mixtures of phosphate buffer (pH 6·98; 25 ml.) and 20% potassium iodide solution (2 ml.), and the liberated iodine was

[9] Stoehr, *J. prakt. Chem.*, 1893, **47**, 487; 1895, **51**, 464.

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titrated with 0·01N-sodium thiosulphate with starch as indicator.[10] Acid liberated during the oxidation was determined [11] by taking samples from the oxidation mixture and from the blank, adding ethylene glycol (2 ml.), and after 10 min. titrating the whole with 0·01N-sodium hydroxide (Methyl Red, screened with Methylene Blue). Formaldehyde liberated was determined colorimetrically with chromotropic acid,[12] D-glucose being used as standard. Primary amines formed during the oxidation of 2-methyl-5-D-*arabo*-tetrahydroxybutyl-3-D-*erythro*-trihydroxypropylpyrazine was estimated [13] by transferring samples (1 ml. portions) from the oxidation mixture and from the control into centrifuge tubes containing 10% aqueous lead dithionate solution (1 ml.). After mixing and centrifugation, 1 ml. portions of the supernatant liquor were placed in boiling tubes containing distilled water (5 ml.). 0·1% Ethanolic ninhydrin solution (1 ml. portions) was added and the tubes were left in boiling water for 20 min. in the dark. The tubes were cooled to room temperature and their contents were transferred into graduated flasks (10 ml.) which were then filled to the mark with distilled water. The absorption at 570 mμ was read on a colorimeter (Ilford, filter 626). Ethylenediamine was used for the preparation of the standard curve. The results are given in the Table.

Results of periodate oxidation.

	Time (hr.):	1/2	1	2	4	6	9	CH_2O *
(IV)	Uptake *	2·74	2·77	2·80	2·93	2·97	3·17	0·985
	Acid *	1·59	1·79	1·79	1·79	1·99	2·10	
(VIII)	Uptake	6·83	7·17	7·60	7·90	8·00	8·15	1·98
	Acid	3·49	3·91	4·04	4·18	4·67	4·80	
	NH_3 †	—	0·0	0·18	0·35	0·24	0·05	
(XI)	Uptake	5·10	5·35	5·37	5·42	5·55	5·86	1·67
	Acid	3·10	3·22	3·22	3·37	3·70	3·85	

* Moles/mole of the compound oxidised. † Equiv./mole of the compound oxidised.

THE UNIVERSITY, KHARTOUM, SUDAN. [*Received, November 15th,* 1960.]

[10] Neumüller and Vasseur, *Arkiv Kemi*, 1953, **5**, 235.
[11] Halsall, Hirst, and Jones, *J.*, 1947, 1427.
[12] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.
[13] Moore and Stein, *J. Biol. Chem.*, 1948, **176**, 367.

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477. *Thermochemistry of Organoboron Compounds. Part VI.* The Heats of Reaction of Diborane with Olefins.*

By J. E. BENNETT and H. A. SKINNER.

The heats of addition of diborane to the olefins hex-1-ene, hept-1-ene, oct-1-ene, and oct-2-ene have been measured in an isothermal-jacket calorimeter. The heats of reaction were used in conjunction with the already-known heats of formation of diborane and of the olefins to derive values for the heats of formation of the trialkylboranes trihexylborane, triheptylborane, trioctylborane, and tri-s-octylborane.

BROWN and SUBBA RAO [1] recently reported that diborane adds to olefins rapidly at room temperature in the presence of organic ethers to form trialkylboranes in high yields:

$$6RCH{:}CH_2 + B_2H_6 \longrightarrow 2(RCH_2{\cdot}CH_2)_3B \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

The thermochemistry of this reaction provides a route to the heats of formation of the trialkylboranes since the heats of formation of diborane and of the olefins are already well established. Furthermore, the measured heats of combustion of alkylboranes are difficult to interpret accurately because of the tendency towards incomplete combustion of the boron to boric oxide. The alternative route to heats of formation through heats of hydroboronation therefore seemed well worthy of investigation.

* Part V, *J.*, 1954, 3930.

[1] Brown and Subba Rao, *J. Org. Chem.*, 1957, **22**, 1136; *J. Amer. Chem. Soc.*, 1959, **81**, 6428.

An account of some preliminary studies by Bennett and Pedley on the heats of hydroboronation of hex-1-ene, oct-1-ene, and oct-2-ene was presented at the Symposium on Thermodynamics at Wattens in 1959.[2]

Experimental

Preparation of Compounds.—Diborane. This was prepared from sodium borohydride and boron trifluoride etherate in diethylene glycol dimethyl ether (" Diglyme "), as described by Brown and Rao.[1] The diborane gas was purified by low-temperature bulb-to-bulb fractional distillation in an all-glass grease-free vacuum system. Samples of diborane were freshly prepared before each hydroboronation in quantities of 100—150 ml., sufficient for a single calorimetric experiment only. The diborane samples were used immediately after preparation.

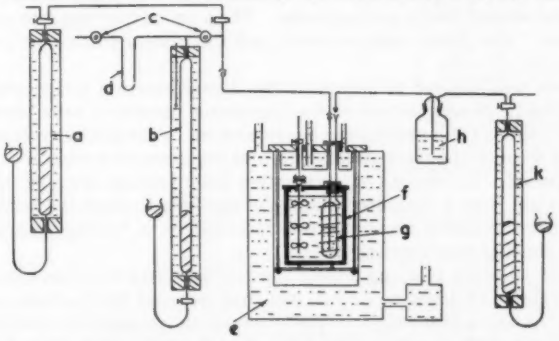
Diethylene glycol dimethyl ether. This, supplied by the Ansul Chemical Co., was purified by distillation over calcium hydride under reduced pressure (20 mm., glass-ring packed column): the main fraction was redistilled over lithium aluminium hydride and the purified product stored under dry oxygen-free nitrogen.

Hex-1-ene. The hexene was supplied by the N.C.L., D.S.I.R., Teddington, and was stated to be >99·9% pure hex-1-ene. A further sample, supplied by Light and Co., was purified as described under hept-1-ene.

Hept-1-ene. This material, supplied by Light and Co., was purified by distillation from sodium, followed by careful fractional distillation using an 18-in. gauze-packed column.

Oct-1-ene and oct-2-ene. These were also supplied by Light and Co. and were purified in the same manner as hept-1-ene. Measurements of the purity of the olefins were made by Mr.

Fig. 1. a, Nitrogen burette; b, Diborane burette; c, Springham valves; d, U-Tube; e, Thermostat jacket; f, Calorimeter can; g, Reaction vessel; h, Acetone-filled trap; k, Exit-gas burette.



J. V. Davies, using the melting-point calorimeter of Brooks and Pilcher.[3] The hept-1-ene had a purity of 99·28 ± 0·1 mole %, and oct-1-ene a purity of 98·4 ± 0·2 mole %. The oct-2-ene contained both the *cis*- and the *trans*-form, but the relative proportions were not determined.

Calorimeters. A calorimetric experiment was carried out by measuring the temperature change of the calorimeter when a carefully measured volume of diborane gas was passed into a solution of olefin in Diglyme solvent contained in a Pyrex-glass vessel inside the calorimeter. The calorimeter was of the constant-temperature environment type, and is shown schematically in Fig. 1. The calorimeter can (polished copper; capacity 1·4 l.) was placed centrally in the well of a surrounding jacket thermostat, maintained at 25·0°. The roof of the thermostat well was closed by a thermostatted lid, also maintained at 25°.

The calorimeter can was fitted with a propeller stirrer, an electric heater for calibration purposes, and a shielded thermistor element (Stantel F/2311) acting as resistance thermometer. In each experiment the can was charged with 1200 g. of water, and sealed with a close-fitting copper lid. This was slotted to take the inlet and exit tubes of the glass reaction vessel, and to support the vessel firmly in position inside the can.

The experimental procedure was as follows: the reaction vessel (capacity 50 ml.) was

[2] Skinner, Bennett, and Pedley, Symposium on Thermodynamics, Paper 3: Wattens, Aug. 1959.
[3] Brooks and Pilcher, *J.*, 1959, 1535.

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cleaned, thoroughly swept out with pure dry nitrogen, and charged with 35 ml. of " Diglyme " solvent. The vessel was fitted in position inside the calorimeter can, which, in turn, was placed centrally in the thermostat jacket. The calorimeter stirrer was set in motion, and the inlet and exit tubes to the reaction vessel were connected through ball-and-socket joints to the inlet and exit gas lines. Nitrogen from a storage burette was passed *via* the inlet gas line into the reaction vessel, escaping *via* the exit gas line to an acetone-filled trap backing the calorimeter, and thence to a gas burette. The nitrogen was passed for several minutes in order thoroughly to sweep trapped air from the system.

Diborane from the preparative apparatus was transferred by vacuum distillation to a U-tube, cooled by liquid air, and the frozen diborane subjected to high-vacuum pumping for several minutes to remove traces of hydrogen gas impurity. The sample was then cut off from the vacuum-line and preparative apparatus by closing a Springham greaseless valve in the connecting-line (Springham valves were found to be satisfactory for work with diborane). The diborane was allowed to warm and expand as a gas into the storage gas-burette.

At this stage the solvent in the calorimeter reaction vessel was *pretreated* with diborane by forcing a measured volume of the gas from the burette into it. This pretreatment was very necessary to remove traces of moisture and other hydroxylic impurities (*e.g.*, glycol residues) present in the diethylene glycol dimethyl ether. Diborane escaping from the reaction vessel was absorbed in the acetone trap; the hydrogen gas formed by reaction of the diborane with impurities in the solvent passed the trap to be collected in a gas-burette on the exit side. A slight evolution of hydrogen gas indicated a clean dry sample of solvent; a moist sample, on the other hand, required an extensive pretreatment before hydrogen evolution ceased. After the diborane pretreatment the solvent was swept out with nitrogen to remove diborane from the system.

The inlet to the reaction vessel was now opened at the ball-joint, and 6—7 ml. of olefin was introduced into the solvent from a micropipette. The acetone trap was removed and replenished with fresh acetone. The joints were re-made, and the system was swept out once more with dry nitrogen.

The calorimeter was allowed to approach the desired starting temperature and to reach a steady thermal state. Measurements of the thermistor resistance were then taken at regular time intervals to establish the pre-rating characteristics. A measured volume of diborane was now slowly forced through the reaction mixture, and the thermistor resistance recorded throughout the reaction period. At the end of the reaction (after passage of *ca.* 80 ml. of diborane), the system was swept out with a measured volume of nitrogen to clear the inlet lines of diborane, following which the thermistor resistance was recorded for a further period of *ca.* 20 min. to establish the after-rating characteristics.

The amount of diborane reacting during the reaction period in the calorimeter was determined from the volume of diborane added, less that escaping the reaction zone, subsequently to be absorbed in the exit acetone trap. This latter was determined by hydrolysing the contents of the trap at the end of the reaction, and estimating the boric acid produced. Generally, less than 2% of the added diborane escaped unchanged from the reaction zone.

In addition to the heats of hydroboronation, measurements were also made of the heats of solution of products and reactants in diethylene glycol dimethyl ether. A small Dewar vessel calorimeter (150 ml. capacity), fitted with a flange and closed by a brass headpiece, through which passed a rotary stirrer, thermistor element, calibration heater, and solution pipette, was used to measure the heats of mixing of the olefins with the solvent. This calorimeter was not suitable for measuring heats of solution of the alkylboranes, which, because of their extremely ready oxidation by air, had to be handled in a completely sealed, nitrogen-filled system. The calorimeter used is shown in Fig. 2. The Pyrex reaction vessel (200 ml. capacity) contained a stainless-steel stirrer, fitting through a greased ball-joint, an ampoule-holder and breaking-device, and a central well to accommodate the thermistor element.

The solution vessel was placed centrally in a copper can and surrounded completely by a thermally insulating polyurethane foam (formed in *situ* and allowed to set hard).

In a measurement of the heat of solution, a glass ampoule containing a known weight of pure alkylborane was broken under the surface of 200 ml. of solvent in the solution vessel, and the resulting change in resistance of the thermistor element recorded. Before the bulb was broken, the solvent was pretreated with a small amount of diborane gas in order to destroy traces of peroxidic material or of dissolved oxygen, and then thoroughly swept out with pure

nitrogen. This pre-treatment was necessary—otherwise the mixing (which is actually an endothermic process) was masked by spurious exothermic oxidation side-reactions.

Calibration.—The reaction calorimeter (Fig. 1) was calibrated electrically by the substitution method. The mean value (9 calibration experiments) of the calibration constant, k, was $94{\cdot}22 \pm 0{\cdot}15$—where $k \log R_i/R_f$ = heat evolved in calories, and R_i, R_f are the initial and final resistances of the thermistor ($\log R_i/R_f \propto \Delta T$ = corrected temperature rise of the calorimeter). The heat exchange between calorimeter and jacket was evaluated from the resistance–time curves by applying Regnault and Pfaundler's method.

The solution calorimeters were also calibrated electrically.

Units and Assumed Data.—Heat quantities are given throughout in thermochemical calories,

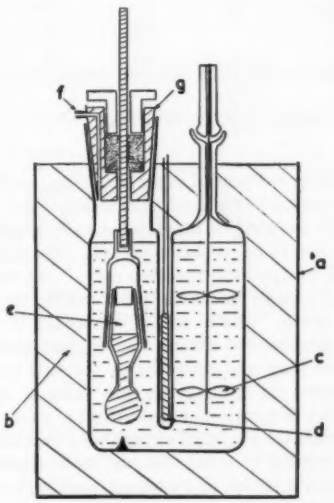

FIG. 2. a, Copper can; b, Foam insulation; c, Steel stirrer; d, Thermistor; e, Ampoule and holder; f, Nitrogen inlet; g, Brass cone valve.

defined by 1 cal. ≡ 4·1840 abs. joules. All measurements were made so that the final calorimeter temperature was 25° c.

To calculate the mass of diborane from the volume used, it was assumed that 1 mole of *pure* diborane occupies 22·15 l. at N.T.P. The purity of the diborane samples used in each experiment was not measured, but analyses were made of selected diborane samples (by hydrolysing a measured volume, and estimating the boric acid produced) which indicated a purity range of 99—99·5%. We have assumed, somewhat arbitrarily, that 1 mole of diborane was contained in 22·4 l. (at N.T.P.) of the gas taken from the diborane burette.

The value adopted for the standard heat of formation of diborane is that reported by Prosen, Johnson, and Pergiel [4] from measurements of the heat of decomposition into amorphous boron and hydrogen gas, ΔH_f° (B_2H_6, gas) = $6{\cdot}73 \pm 0{\cdot}52$ kcal./mole.

The heats of formation of the liquid olefins were obtained from heat of combustion and heat of vaporization data given in the A.P.I. Tables (Project 44), published by the Carnegie Institute of Technology, Pittsburgh:

$$\Delta H_f^\circ \text{ (hex-1-ene, liq.)} = -17{\cdot}30 \text{ kcal./mole}$$
$$\Delta H_f^\circ \text{ (hept-1-ene, liq.)} = -23{\cdot}41 \text{ kcal./mole}$$
$$\Delta H_f^\circ \text{ (oct-1-ene, liq.)} = -29{\cdot}52 \text{ kcal./mole}$$

The heat of formation values for *cis*- and *trans*-oct-2-ene were estimated on the basis of the known values for hept-2-ene and hex-2-ene,

$$\Delta H_f^\circ \text{ (}cis\text{-oct-2-ene, liq.)} = -31{\cdot}12 \text{ kcal./mole}$$
$$\Delta H_f^\circ \text{ (}trans\text{-oct-2-ene, liq.)} = -32{\cdot}12 \text{ kcal./mole}$$

[4] Prosen, Johnson, and Pergiel, *J. Res. Nat. Bur. Stand.*, 1958, **61**, 247.

The error limits associated with the $\Delta H_f°$ values of the olefins are of the order of $\pm 0{\cdot}2$—$0{\cdot}3$ kcal./mole.

Test of the Calorimeter.—A test of the calorimeter was made by measuring the heat of hydrolysis of diborane gas. The reaction vessel was filled with 40 ml. of water, and a measured volume of diborane passed through it. About 80% of the diborane was hydrolysed in the reaction vessel, the remainder being carried away by the hydrogen evolved, subsequently to be absorbed outside the calorimeter in two acetone-filled traps. The amount of diborane hydrolysed in the calorimeter was determined by estimating the boric acid formed in the reaction vessel. The measured heat of hydrolysis (based on the amount of boric acid formed in the calorimeter) was $\Delta H = -112{\cdot}5 \pm 1{\cdot}5$ kcal./mole, which is in very fair agreement with the more precise measurements made by Prosen, Johnson, and Pergiel [5] and by Gunn and Green.[6]

Results

Hex-1-ene.—The reaction occurring in the calorimeter was assumed to follow the equation:

$$B_2H_6(\text{gas}) + (m + 6)C_6H_{12}\ (\text{" Diglyme " soln.}) \longrightarrow 2B(C_6H_{13})_3 + mC_6H_{12}\ (\text{" Diglyme " soln.}) \quad . \quad . \quad (2)$$

The observed heat of reaction, $\Delta H_{obs.}$, refers to this system; in most experiments an approximately twofold excess of hexene was used.

The amount of reaction in each experiment was determined from the amount of diborane consumed in the reaction vessel. Reaction (2) is rapid, and only a small fraction of the diborane added escaped the reaction zone. As already stated, the " Diglyme " solvent was pretreated with diborane before the calorimetric experiment proper in order to remove impurities particularly water, which would otherwise compete with reaction (2). As a check on this, any hydrogen formed during the reaction period and escaping from the reaction vessel and backing acetone trap was collected in the exit gas-burette. Since 1 ml. of diborane produces 6 ml. of hydrogen on hydrolysis, the volume of gas evolved during the reaction periods gave a sensitive indication of the extent of competing hydrolysis reactions. In the event of a copious evolution of gas, the experiment was discounted; small corrections were made to $\Delta H_{obs.}$ to allow for the thermal effect of the competing side-reactions, if necessary (based on $\Delta H = -112$ kcal. per 6 moles of hydrogen evolved). The adjusted values are listed as $\Delta H_{corr.}$.

Separate measurements were made of the heats of solution of hexene and of trihexylborane in " Diglyme." From the measured heats of solution, adjustments were made to $\Delta H_{corr.}$ in order to derive the heat of the idealised reaction, ΔH_2:

$$B_2H_6\ (\text{gas}) + 6C_6H_{12}\ (\text{liq.}) \longrightarrow 2B(C_6H_{13})_3\ (\text{liq.}) \quad . \quad . \quad . \quad . \quad (3)$$

A representative selection from the experimental results is presented in Table 1.

Table 1. *Reaction of diborane with hex-1-ene.*

	1	2	3	4
Diborane added (mmoles)	3·569	3·226	3·690	3·801
Diborane escaping reaction	0·069	0·024	0·027	0·027
Diborane consumed	3·500	3·202	3·663	3·774
Hexene added (mmoles)	47	32	28	33
Hexene excess	26	13	6	10
Gas evolved (ml.)	nil	nil	nil	nil
$\Delta H_{obs.}$, kcal./mole B_2H_6	−138·7	−136·6	−135·3	−136·6
$\Delta H_{corr.}$, kcal./mole of B_2H_6	−138·7	−136·6	−135·3	−136·6
$\Delta H_{soln.}$, kcal./6 moles of hexene	3·8	4·1	4·2	4·1
$\Delta H_{soln.}$, kcal./2 moles of BHx_3	3·8	3·8	3·8	3·8
ΔH_2, kcal./mole of B_2H_6	−138·7	−136·3	−134·9	−136·3

Mean $\Delta H_2 = -136{\cdot}6$ kcal./mole. Standard deviation of mean $= \pm 0{\cdot}8$ kcal./mole.

Hept-1-ene, Oct-1-ene, and Oct-2-ene.—Selected results on the hydroboration of hept-1-ene, oct-1-ene, and oct-2-ene are presented in Table 2. The oct-2-ene used in these experiments was a purified commercial sample, containing the *cis*- and the *trans*-isomer in proportions that were not determined.

[5] Prosen, Johnson, and Pergiel, *J. Res. Nat. Bur. Stand.*, 1959, **62**, 43.
[6] Gunn and Green, *J. Phys. Chem.*, 1960, **64**, 61.

Individual corrections to heats of solutions are not listed in Table 2. The measurements on trihexylborane and hexene in " Diglyme " showed that $\Delta H_{soln.}$ of trihexylborane is approximately equal to $\Delta H_{soln.}$ of three moles of hexene—so that, in effect, the corrections to the heats of solution needed to obtain ΔH_2 from $\Delta H_{obs.}$ cancel out. A cancellation of the corrections has been *assumed* for the examples listed in Table 2.

TABLE 2. *Reaction of diborane with hept-1-ene, oct-1-ene, and oct-2-ene.*

	Hept-1-ene			Oct-1-ene		
Diborane added (mmoles)	3·703	4·015	4·033	3·547	3·641	3·609
Diborane escaping	0·040	0·050	0·060	0·025	0·026	0·030
Diborane consumed	3·663	3·965	3·976	3·522	3·615	3·579
Olefine added (mmoles)	32	34	34	38	33	34
Olefin excess	10	10	10	16	11	12
Gas evolved (ml.)	—	3	1	6	—	12
$\Delta H_{obs.}$ (kcal./mole of B_2H_6)	−135·5	−135·8	−134·8	−134·5	−136·6	− 135·3
$\Delta H_{corr.}$	−135·5	−135·9	−134·8	−134·8	−136·6	−135·8
ΔH_2, mean value		−135·4			−135·7	
Standard deviation		±0·4			±0·5	

	Oct-2-ene				
Diborane added (mmoles)	3·922	3·806	2·323	3·788	3·739
Diborane escaping	0·044	0·047	0·010	0·045	0·050
Diborane consumed	3·878	3·759	2·314	3·743	3·689
Olefine added (mmoles)	32	35	30	33	33
Olefin excess	9	12	16	10	11
Gas evolved (ml.)	12	22	—	—	12
$\Delta H_{obs.}$ (kcal./mole of B_2H_6)	−116·0	−116·0	−118·4	−115·4	−115·4
$\Delta H_{corr.}$	−116·1	−116·2	−118·4	−115·4	−115·5
ΔH_2, mean value			−116·3		
Standard deviation			±0·55		

DISCUSSION

The ΔH_2 values in Tables 1 and 2, together with the accepted heats of formation of diborane and of the olefins, provide the data needed to calculate the heats of formation of the alkylboranes through the thermochemical equation appropriate to the idealized hydroboronation reaction, *viz*:

$$\Delta H_f^\circ \text{ (trialkylborane, liquid)} = \tfrac{1}{2}\Delta H_f^\circ \text{ (B_2H_6, gas)} + 3\Delta H_f^\circ \text{ (olefin, liquid)} + \tfrac{1}{2}\Delta H_2 \quad . \quad . \quad . \quad (4)$$

The values calculated from eqn. (4) are listed below: the limits of error recorded represent the uncertainty intervals taking into account the spread in the experiment results, the standard deviation in calibration experiments, and the uncertainties in assumed data on heats of formation.

	kcal./mole		kcal./mole
ΔH_f° (trihexylborane, liq.)	−116·83 ± 2·2	ΔH_f° (trioctylborane, liq.)	−153·04 ± 1·8
ΔH_f° (triheptylborane, liq.)	−134·56 ± 1·7	ΔH_f° (tri-s-octylborane, liq.) ...	−149·25 ± 3·5

The value calculated for boron tri-s-octylborane is based on the assumption that the oct-2-ene contained equal amounts of the *cis*- and the *trans*-form: the uncertainty interval makes allowance for this lack of knowledge of the true composition.

Measurements of the heats of combustion of triethylborane and of tributylborane have been reported in a preliminary communication by Prosen and Johnson.[7] The combustion data lead to $\Delta H_f^\circ = -83{\cdot}9$ kcal./mole for liquid tributylborane, and $\Delta H_f^\circ = -46{\cdot}8$ kcal./mole for liquid triethylborane. Accepting the constant heat of combustion increment per methylene group obtained from combustion studies on liquid hydrocarbons containing six or more carbon atoms, and adding this to Prosen and Johnson's combustion data on tributylborane, yields an estimated $\Delta H_f^\circ = -120{\cdot}5$ kcal./mole for liquid trihexylborane.

[7] Prosen and Johnson, reported by Wagman, Munson, Evans, and Prosen, *N.B.S. Report*, No. 3456, 1954.

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Prosen and Johnson have not stated the error limits attached to their preliminary combustion studies on tributylborane: they may be substantial, however, because of the difficulties of complete analysis of the products of combustion, and a figure as large [8] as ±3 kcal./mole is possible. The estimated $\Delta H_f°$ for trihexylborane can, in this event, be said to agree (within the combined error limits of both investigations) with the value reported here. A more detailed comparison must await the complete account of the measurement of heats of combustion.

Haseley, Garrett, and Sisler [9] have recently reported measurements of the heat of combustion in a bomb calorimeter of liquid tri-s-butylborane, from which they derived $\Delta H_f°$ [B(s-butyl)$_3$, liq.] = −75 ± 6 kcal./mole. From the difference between this and the heat of formation of tributylborane given by Prosen and Johnson, the isomerization process

$$BBu^n_3 \longrightarrow BBu^s_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

is calculated to be endothermic, ΔH = 8·9 kcal./mole: the uncertainty in ΔH, however, is possibly as large as ΔH itself. The present investigation leads to a similar conclusion in respect of the isomerization

$$BOct^n_3 \longrightarrow BOct^s_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

for which ΔH is calculated to be 3·8 kcal./mole—but once again, the uncertainty is as large as ΔH itself. Nevertheless, the possibility that chain branching in alkylboranes leads to diminished thermochemical stability relative to the n-alkylboranes is interesting. Brown and Subba Rao [10] have already drawn attention to the ready isomerization of branched-chain alkylboranes to form, as they say, the " more stable " tri-n-alkylboranes (*i.e.*, with boron at the terminal position in the alkyl chain).

An isomerization process of paraffin hydrocarbons similar to scheme (5) from the steric point of view is the change:

$$\text{4-}n\text{-propylheptane} \longrightarrow \text{2,4-dimethyl-3-isopropylpentane} \quad . \quad . \quad . \quad (7)$$

In this case, the available data on heats of formation indicate that the isomerization is exothermic, ΔH = −1·6 kcal./mole (reactants in the liquid state). Hence, in so far as similar isomerization processes of trialkylboranes are *endothermic*, this would not seem to be due simply to steric factors.

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MANCHESTER 13. [*Received, December* 30*th*, 1960.]

[8] W. H. Johnson, personal communication.
[9] Haseley, Garrett, and Sisler, *J. Phys. Chem.*, 1956, **60**, 1136.
[10] Brown and Subba Rao, *J. Amer. Chem. Soc.*, 1959, **81**, 6434.

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478. 4-*Substituted Steroids Derived by Rearrangement and Reduction of Cholestenone Enol Acetate.*

By B. R. BROWN, P. W. TROWN, and J. M. WOODHOUSE.

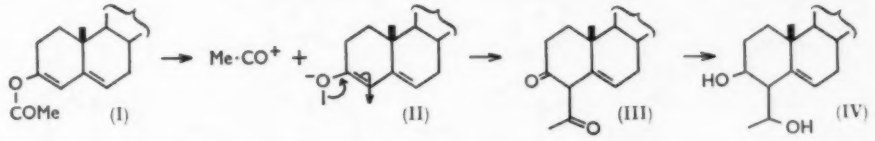
One of the diols produced by the simultaneous action of lithium aluminium hydride and aluminium chloride on cholestenone enol acetate is shown to be 4α-1′-hydroxyethylcholest-5-en-3β-ol. Another is probably 4β-1′-hydroxyethylcholest-5-en-3α-ol.

THE simultaneous action of lithium aluminium hydride and aluminium chloride on the enol acetate (I) of cholest-4-en-3-one was previously reported [1] to yield 36% of material soluble in light petroleum [shown to be a mixture of cholest-4-ene (16%) and cholestenone (20%)] and 49% of material insoluble in light petroleum which, by crystallisation, yielded a

[1] Brown, *J.*, 1952, 2756.

molecular compound of two diols, designated (A) and (B). It was tentatively suggested that these diols were cholest-5-ene-3α,4β- and -3β,4α-diol, which at that time were unknown. This suggestion is now known to be incorrect, since Fieser and Stevenson [2] have prepared and proved the structure of cholest-5-ene-3β,4α-diol which differs from both the diols (A) and (B).

Since the reduction is carried out in the presence of aluminium chloride, the isomeric diols might be expected to arise by rearrangement of the enol acetate and subsequent reduction as shown in the annexed scheme. The rearrangement envisaged is formally analogous to the Fries rearrangement. The acetylium ion attacks the 4-position of the



enolate ion (II), evidence for the existence of which during the reduction of cholestenone enol acetate with lithium aluminium hydride has been advanced by Dauben and Eastham.[3] The resulting diketone (III) is reduced by lithium aluminium hydride to give the 4-1′-hydroxyethylcholest-5-en-3-ol structure (IV). The work described here substantiates structure (IV) for the diols (A) and (B).

This structure requires a molecular formula of $C_{29}H_{50}O_2$, whereas in the earlier paper [1] the analyses were calculated on the formula $C_{27}H_{46}O_2$. The differences in the carbon and hydrogen percentages calculated for the diols and their simple derivatives on the C_{27} and C_{29} formulæ are almost within the experimental error of analysis. However, the results now recorded show better agreement with the C_{29} formula and analyses of more complex derivatives [*e.g.*, the cyclic sulphite ester and two bromo-compounds of diol (B) and the toluene-*p*-sulphonate ester of diol (A)] allow a definite distinction and permit only the C_{29} formula.

The presence [1] of a double bond in diol (B) has been confirmed by the observation that this diol reacts with bromine in chloroform. However, the only pure product isolated was a bromo-ether (V), formally derived by loss of hydrogen bromide from the diol dibromide. The difficulty experienced in hydrogenating this double bond [1] is explicable in terms of the proposed structure where a large hindering group is at position 4.

The suspected presence of a CH_3·CH·OH group in the diols led to the use of hypohalite as an oxidising agent. Both diols with potassium hypobromite in aqueous dioxan yielded cholest-4-en-3-one and the presence of bromoform in the products was demonstrated by a sensitive colour test.[4] The production of cholestenone indicates that the CH_3·CH·OH group is adjacent to a 3-hydroxyl group since oxidation and loss of bromoform must lead to a carboxylic acid which can readily lose carbon dioxide (see annexed scheme).[5] Further, the double bond must be in either the 4,5- or the 5,6-position; the latter is favoured by the negative rotations of the diols and their derivatives. Attachment of the CH_3·CH·OH group to the 2-position would explain the formation of cholestenone: however, degradation of diol (B) to a hydrocarbon and synthesis of the latter have shown that the attachment is at the 4-position in this diol.

Treatment of diol (B) with phosphorus tribromide gave the dibromo-compound (VI), which with lithium and liquid ammonia gave an ethylcholestene (VII) which melted over a range. A similar reduction of cholesteryl bromide gave material which melted over a

[2] Fieser and Stevenson, *J. Amer. Chem. Soc.*, 1954, **76**, 1728.
[3] Dauben and Eastham, *J. Amer. Chem. Soc.*, 1953, **75**, 1718.
[4] Clarke, " A Handbook of Organic Analysis," Edward Arnold and Co., London, 4th edn., 1926, p. 67.
[5] Cf. Simonsen and Ross, " The Terpenes," Cambridge Univ. Press, 1957, Vol. V, p. 451.

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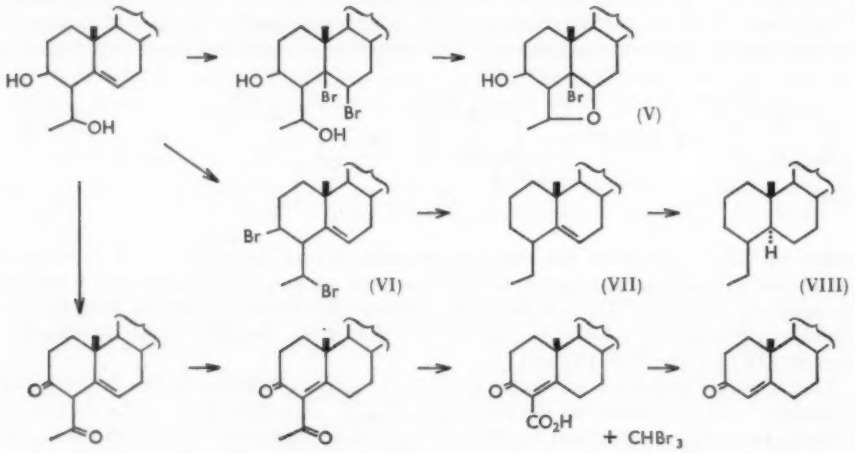
range below the m. p. of cholest-5-ene and had a more positive specific rotation than cholest-5-ene; repeated crystallisation of this material gave pure cholest-5-ene. Hydrogenation of the crude ethylcholestene over platinum in ether–acetic acid gave a hydrocarbon (VIII), $[\alpha]_D$ +6°, which melted sharply at 89—90°. It seems, from these observations, that reduction of an unsaturated halogeno-steroid by lithium and liquid ammonia may give rise to some of the saturated hydrocarbon along with the unsaturated hydrocarbon. The



saturated hydrocarbon (VIII) from diol (B), which differed from cholestane itself, was expected to be either 4α- or 4β-ethylcholestane, since reduction of a cholest-5-ene in acid solution usually leads to a *trans*-A/B ring junction.

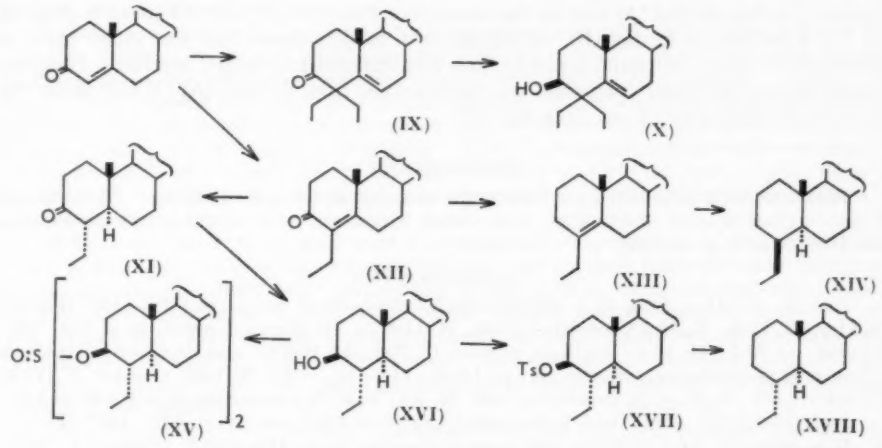
The two 4-ethylcholestanes have been synthesised in order to establish the structure and stereochemistry of the saturated hydrocarbon derived from diol (B). Despite statements to the contrary,[6-9] Atwater [10] has reported that steroidal 4-en-3-ones can be successfully monomethylated at the 4-position. By following Atwater's procedure, but using a higher dilution and a longer reaction time, we have ethylated cholest-4-en-3-one directly, using ethyl iodide and potassium in t-butyl alcohol, and we isolated 4-ethylcholest-4-en-3-one (XII) (54%), 4,4-diethylcholest-5-en-3-one (IX) (10%), and unchanged cholestenone (33%). The diethyl-ketone (IX) has zero rotation, but lithium aluminium hydride reduces it to 4,4-diethylcholest-5-en-3β-ol (X), $[\alpha]_D$ −57°.

Reduction of 4-ethylcholestenone as described by Djerassi *et al.*[9] gave 4α-ethylcholestan-3-one (XI), known to have this configuration by analogy with 4α-methylcholestan-3-one.[6,7] Further reduction of the ethylcholestanone gave 4α-ethylcholestan-3β-ol (XVI),[9] which even with hot thionyl chloride gave a sulphite ester (XV). However, reduction of the toluene-*p*-sulphonate (XVII) with lithium aluminium hydride gave 4α-ethylcholestane (XVIII), m. p. 89—90°, $[\alpha]_D$ +4·5°. The hydrocarbon obtained from diol (B) caused no depression of m. p. when admixed with 4α-ethylcholestane, and the two have almost identical specific rotations. This result establishes that the CH_3·CH·OH group in diol (B) is attached at the 4-position and has the α-configuration.

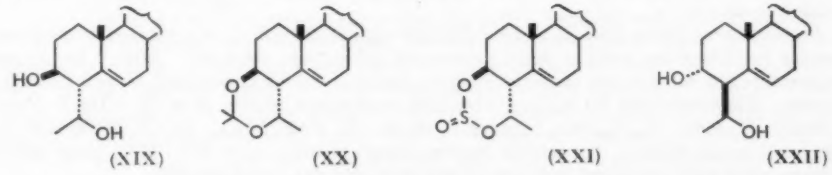
Reduction of 4-ethylcholest-4-en-3-one (XII) with lithium aluminium hydride and aluminium chloride [11] gave 4-ethylcholest-4-ene (XIII), which, on catalytic hydrogenation

[6] Meakins and Rodig, *J.*, 1956, 4679.
[7] Beton, Halsall, Jones, and Phillips, *J.*, 1957, 753.
[8] Mazur and Sondheimer, *J. Amer. Chem. Soc.*, 1957 **79**, 2906.
[9] Djerassi, Cais, and Mitscher, *J. Amer. Chem. Soc.*, 1958, **80**, 247.
[10] Atwater, *J. Amer. Chem. Soc.*, 1957, **79**, 5315.
[11] Broome and Brown, *Chem. and Ind.*, 1956, 1307.

in ether–acetic acid, afforded 4β-ethylcholestane (XIV), m. p. 75—77°, $[\alpha]_D$ +31°. This hydrocarbon is assigned this configuration since acidic conditions favour the formation of a cholestane system [12] and *cis*-addition of hydrogen then leads to a 4β-derivative.[13]



Consideration of the infrared spectra of the diols and their acetates in carbon disulphide has enabled the stereochemistry of the 3-hydroxyl groups to be deduced. The absorptions



recorded in Table 1 are due to C–O stretching vibrations and the work of Jones *et al.*,[14] Cole,[15] and Page [16] leads to the assignments of stereochemistry shown. Thus diol (B) is 4α-1′-hydroxyethylcholest-5-en-3β-ol (XIX). Further, the results recorded in Table 2

TABLE 1. *Infrared spectra of the diols and their acetates in* CS_2 *solution.*

Compound	Frequency ($cm.^{-1}$)	Confign. of 3-OH or 3-AcO-group	Compound	Frequency ($cm.^{-1}$)	Confign. of 3-OH or 3-AcO-group
Diol (A)	1006	axial, 3α	Diol (B) diacetate	1028	equat., 3β
Diol (B).....	1049	equat., 3β	Diol (A) diacetate	1242, 1211	axial, 3α
Diol (A) diacetate	1016	axial, 3α	Diol (B) diacetate	1242 only	equat., 3β

TABLE 2. OH *Stretching frequencies of the diols in* CS_2 *solution.*

		Absorption bands ($cm.^{-1}$)					Absorption bands ($cm.^{-1}$)		
Diol	Concn. (mg./ml.)	Free OH	Intramol. H-bond	Intermol. H-bond	Diol	Concn. (mg./ml.)	Free OH	Intramol. H-bond	Intermol. H-bond
A	9	3610m sh	—	—	B	9	3620w sh	3520m sh	3300m br
A	20	3610m sh	—	3310w br	B	20	3620w sh	3520m sh	3300s br
B	4	3620w sh	3520m sh	3300w br					

[12] Windaus, *Ber.*, 1919, **52**, 170.
[13] Mazur and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.
[14] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1951, **73**, 3215.
[15] Cole, *J.*, 1952, 4969.
[16] Page, *J.*, 1955, 2017.

XUM

show that diol (B) is intramolecularly hydrogen-bonded, a conclusion confirmed by the consideration of a model of diol (B) and by the preparation of an isopropylidene compound (XX) and a cyclic sulphite ester (XXI).

The infrared evidence leads to the assignment of a 3α-configuration to one of the hydroxyl groups in diol (A) and, on the assumption that the CH_3·CH·OH group is attached at the 4-position as in diol (B), consideration of models shows that this group must be β-orientated if the compound is not to show intramolecular hydrogen bonding. In agreement, an isopropylidene compound was not obtained from the diol (A) (XXII) under the conditions which yielded one from diol (B).

Experimental

Rotations were determined for chloroform solutions at room temperature. Alumina was Spence's grade H or O, deactivated, when stated, with acetic acid. Light petroleum refers to the fraction of b. p. 40—60°.

Degradation of diols

Diol (A) (XXII).—This, 4β-1′-*hydroxyethylcholest*-5-*en*-3α-*ol*, has m. p. 179·5—180° (Found: C, 81·0; H, 11·5. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·6%). It gives a *diacetate*, m. p. 159—160° (Found: C, 77·1; H, 10·5. $C_{33}H_{54}O_4$ requires C, 77·0; H, 10·5%), and *ditoluene*-p-*sulphonate* (from ethanol–methanol), needles, m. p. 141·5—142°, $[\alpha]_D$ −25° (*c* 1·68) (Found: C, 70·3; H, 8·4; S, 8·7. $C_{43}H_{62}O_6S_2$ requires C, 70·0; H, 8·4; S, 8·7%), decomposing in 5 min. at 140°.

Diol (B) (XIX).—This, 4α-1′-*hydroxyethylcholest*-5-*en*-3β-*ol*, has m. p. 179—180° (Found: C, 81·1, 80·6; H, 11·5, 11·7)%, and gives a *diacetate*, m. p. 114—115·5° (Found: C, 76·9; H, 10·4%).

The two diols give a *molecular compound*, m. p. 196—197° (Found: C, 80·75, 81·0; H, 11·55, 11·4%). Both diols and the molecular compound gave a yellow colour with tetranitromethane in chloroform.

Bromo-ether (V) *from Diol* (B).—Diol (B) (249 mg.) in chloroform was treated dropwise with bromine in chloroform until a slight permanent colour was observed. After 2 hr. at room temperature the solvent was removed *in vacuo* and the residue crystallised several times from acetone. The *bromo-ether* (91 mg.) was obtained as colourless needles, m. p. 167—168·5° (Found: C, 68·35; H, 9·85. $C_{29}H_{49}BrO_2$ requires C, 68·35; H, 9·65%), $\nu_{max.}$ (in CS_2) 3400 (OH) and 1098 $cm.^{-1}$ (cyclic ether). The mother-liquors yielded crystals, m. p. 171—174°, whose analysis indicated that they contained both the bromo-ether and the diol dibromide.

Hypobromite Oxidation of the Diols.—To a solution of the diol (A or B) (368 mg.) in dioxan (35 ml.) was added a solution of potassium hypobromite prepared from bromine (1·90 g.), potassium hydroxide (1·06 g.), and water (25 ml.). The resulting suspension was stirred for 3 days. Excess of 2N-sulphuric acid was added and the products were removed in ether. The extract was washed with water, sodium thiosulphate solution, sodium carbonate solution, and water to neutrality. A portion (1 ml.) of this extract was boiled with a little pyridine and an equal volume of sodium hydroxide solution. The pyridine layer became deep red, indicating the presence of bromoform.[4] Control experiments showed that the other reagents present did not interfere with this test.

Evaporation of the extract gave a residue which was dissolved in ethanol and boiled with sodium iodide for 1·5 hr. Addition of water, extraction with ether, and evaporation of the washed extract gave an oil which was extracted with light petroleum. The residue, on recrystallisation, gave unchanged diol (18 mg.), m. p. and mixed m. p. 179—180°. The light petroleum extract was chromatographed on alumina (grade O), yielding, on elution with benzene, a yellow oil (230 mg.). Part of the oil was sublimed at 180°/0·5 mm.; the crystalline sublimate separated from acetone–methanol as needles, m. p. 79—80°, unchanged on admixture with cholest-4-en-3-one. The infrared spectrum in Nujol was identical with that of authentic cholestenone. The oil gave a 2,4-dinitrophenylhydrazone which separated from ethyl acetate–ethanol as red prisms, m. p. 229—231°; the mixed m. p. with cholestenone dinitrophenylhydrazone was 231—233°; the ultraviolet and infrared spectra were identical with those of cholestenone dinitrophenylhydrazone.

Action of Phosphorus Tribromide on Diol (B).—Phosphorus tribromide (1·97 g.) was added with shaking to a solution of diol (B) (1·01 g.) in chloroform (50 ml.). After 4 days. excess of

water was added and the product isolated by using chloroform. The crude product was washed with acetone to remove a gummy solid (85 mg.) and crystallised several times from ether–methanol. The *dibromo-compound* (VI) (280 mg.) was obtained as colourless needles, m. p. 96·5—98°, $[\alpha]_D$ +17° (*c* 1·08) (Found: C, 62·5; H, 8·5; Br, 28·7. $C_{29}H_{48}Br_2$ requires C, 62·6; H, 8·6; Br, 28·8%).

4α-Ethylcholest-5-ene (VII).—The above dibromo-compound (291 mg.) in ether (60 ml.) was added to lithium (480 mg.) in liquid ammonia (150 ml.) at −35°. After 2 hr. with stirring, ammonium chloride was added and the ammonia was allowed to evaporate. Addition of water and extraction with ether gave a colourless solid which was filtered through alumina (grade O) in light petroleum and crystallised from ethyl acetate–methanol, to yield a solid (153 mg.), m. p. 90—97°, $[\alpha]_D$ −37·5° (*c* 1·18). Three crystallisations from ethyl acetate gave *4α-ethylcholest-5-ene* as needles, m. p. 103—107° (Found: C, 87·5; H, 12·3. $C_{29}H_{50}$ requires C, 87·45; H, 12·55%). The compound gave a deep yellow colour with tetranitromethane in chloroform.

4α-Ethylcholestane (VIII).—The crude 4α-ethylcholest-5-ene (60 mg.) in ether (5 ml.) and acetic acid (10 ml.) was hydrogenated at 19°/765 mm. over platinum oxide (50 mg.). Hydrogen uptake was complete after 2·5 hr. The product (58 mg.) gave no colour with tetranitromethane in chloroform. Filtration of a light petroleum solution through alumina (grade O; 5% deactivated) and recrystallisation from ethyl acetate–methanol gave 4α-ethylcholestane as flat needles, m. p. 89—90°, $[\alpha]_D$ +6° (*c* 0·77) (Found: C, 87·0; H, 13·05. Calc. for $C_{29}H_{52}$: C, 87·0; H, 13·0%). The m. p. was unchanged on admixture of the compound with synthetic 4α-ethylcholestane (see below).

Cholest-5-ene (by P. R. Brooks).—Cholesteryl bromide (720 mg.) in ether (280 ml.) was reduced, as above, with lithium (1·14 g.) in liquid ammonia (560 ml.). The product (593 mg.), m. p. 78·5—80·5°, $[\alpha]_D$ −35° (*c* 1·12), was thrice recrystallised from ether–methanol, to give cholest-5-ene (195 mg.), m. p. and mixed m. p. 91·5—92°, $[\alpha]_D$ −51° (*c* 1·07) (Found: C, 87·3; H, 12·05. Calc. for $C_{27}H_{46}$: C, 87·55; H, 12·45%).

Cyclic Sulphite Ester (XXI) *of Diol* (B).—Diol (B) (1·00 g.) was treated with thionyl chloride (2·00 g.). An immediate reaction occurred and the steroid dissolved. After 24 hr. at room temperature, excess of the reagent was removed under reduced pressure and the residue was filtered through alumina (grade O; 10% deactivated) in light petroleum. The resulting oil was chromatographed on alumina (grade O; 30 g.). Elution with light petroleum yielded an intractable yellow gum (166 mg.) which was not further investigated. Elution with light petroleum–benzene (1 : 1 v/v) gave a solid (633 mg.) which, on crystallisation from ether–methanol and then from acetone–methanol, gave the cyclic *sulphite* (XXI) as colourless prisms, m. p. 122·5—123·5°, $[\alpha]_D$ +41° (*c* 1·23) (Found: C, 73·1, 73·1; H, 10·3, 9·9; S, 6·4. $C_{29}H_{48}O_3S$ requires C, 73·1; H, 10·1; S, 6·7%), $\nu_{max.}$ (in CS_2) 1185 $cm.^{-1}$ (sulphite).

Isopropylidene Derivative (XX) *of Diol* (B).—A suspension of diol (B) (220 mg.) in a 2% solution of hydrogen chloride in acetone (50 ml.) was shaken for 3 hr., to yield a clear solution, which was kept at room temperature for 2 days. Powdered calcium carbonate (4·1 g.) was added with shaking until the mixture was neutral. Filtration and evaporation *in vacuo* gave an oil which was put on alumina (grade O) and eluted with light petroleum–benzene (1 : 1 v/v), to yield the *isopropylidene derivative* (XX) (132 mg.) as a solid which separated from acetone–methanol as needles, m. p. 112—113·5°, $[\alpha]_D$ +28° (*c* 1·27) (Found: C, 82·0; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·7; H, 11·5%).

After 48 hr. under the conditions used for diol (B), diol (A) was recovered unchanged (m. p. and mixed m. p. and infrared comparison) in 80% yield after recrystallisation.

Syntheses

4-Ethylcholest-4-en-3-one (XII).—To a stirred solution of potassium (1·75 g.) and cholest-4-en-3-one (10·0 g.) in dry, refluxing t-butyl alcohol (180 ml.) was added during 7 hr. ethyl iodide (4·10 g.) in t-butyl alcohol (600 ml.). The cold mixture was treated with water (200 ml.) and evaporated at 80° *in vacuo*. The residue was dissolved in ether, potassium iodide was separated by filtration, ether was evaporated from the filtrate, and the residue (10·4 g.) was put on alumina (grade H; 10% deactivated; 1 kg.) in light petroleum. Elution (500-ml. fractions) was as follows: (i) Fractions 1—5 (light petroleum) gave a viscous yellow oil (1·30 g.) whose infrared spectrum showed it to be chiefly dialkylated ketone with some monoalkylated product. (ii) Fractions 6—13 (light petroleum) gave crystals (5·32 g.). (iii) Fractions 14—16 (light

petroleum–benzene, 99 : 1 v/v) gave crystals (0·34 g.). (iv) Fractions 17—19 (light petroleum–benzene, 95 : 5 v/v) gave crystals (0·14 g.). (The infrared spectra of fractions 6—19 showed them to be chiefly monoalkylated ketone.) (v) Fractions 20—21 (benzene) gave crystals (3·30 g.), m. p. 79·5—80·5°, unchanged on admixture with the starting material (infrared spectrum identical with that of cholestenone).

Fractions 6—19 were recrystallised from acetone–methanol (1 : 1 v/v), to give 4-ethylcholestenone (4·38 g.), m. p. 85·5—86·5°, $[\alpha]_D$ +92° (*c* 1·8), $\lambda_{max.}$ (in EtOH) 251 mμ (log ε 4·21), $\nu_{max.}$ (in CS_2) 1675 cm.$^{-1}$. Djerassi *et al.*[9] report m. p. 87—89°, $\lambda_{max.}$ (in EtOH) 251 mμ (log ε 4·07). The *enol acetate* separated from acetone–methanol as needles, m. p. 103—104·5°, $[\alpha]_D$ −100° (*c* 0·92), $\lambda_{max.}$ (in EtOH) 237 mμ (log ε 4·34) (Found: C, 81·8; H, 11·05. $C_{31}H_{50}O_2$ requires C, 81·9; H, 11·0%).

The residue after evaporation of the mother-liquor from the above crystallisation was combined with fractions 1—5, dissolved in light petroleum, and put on alumina (grade H; 10% deactivated; 300 g.). Elution with light petroleum (300 ml. fractions) was as follows: (i) Fractions 1—6 gave a viscous yellow oil (0·985 g.) which from acetone–methanol (1 : 1 v/v) gave *4,4-diethylcholest-5-en-3-one* (IX) (0·68 g.) as needles, m. p. 94·5—95°, $[\alpha]_D$ 0° (*c* 1·12) (Found: C, 84·1; H, 11·85. $C_{31}H_{52}O$ requires C, 84·5; H, 11·8%), $\nu_{max.}$ (in CCl_4) 1708 cm.$^{-1}$ (unconjugated C=O). (ii) Fractions 7—13 gave 4-ethylcholestenone (1·00 g.; from acetone–methanol), m. p. 85·5—86·5°.

4,4-Diethylcholest-5-en-3β-ol (X).—4,4-Diethylcholestenone (117 mg.) was reduced in the usual way with lithium aluminium hydride (500 mg.) in ether. The product separated from acetone as prisms (67 mg.), m. p. 107—108°, $[\alpha]_D$ −57° (*c* 0·91) (Found: C, 83·95; H, 12·5. $C_{31}H_{54}O$ requires C, 84·2; H, 12·3%), $\nu_{max.}$ (in CS_2) 3546 and 1027 cm.$^{-1}$ (β-OH). Jouanneteau and Mentzer [17] record m. p. 126° and $[\alpha]_D$ −56° for this alcohol which they obtained by reduction of an oil said to be 4,4-diethylcholest-5-en-3-one.

4α-Ethylcholestan-3-one (XI).—4-Ethylcholest-4-en-3-one (1·10 g.) in ether (50 ml.) was added dropwise during 10 min. to a stirred solution of lithium (0·55 g.) in liquid ammonia (200 ml.). After 20 min. solid ammonium chloride was added until the blue colour of the solution was discharged, ammonia was allowed to evaporate, and water (100 ml.) was added. Extraction with ether and crystallisation from methanol or ethanol gave the saturated ketone (0·81 g.) as plates, m. p. 120·5—121°, $[\alpha]_D$ +33° (*c* 3·83), $\nu_{max.}$ (in $CHCl_3$) 1720 cm.$^{-1}$. Djerassi *et al.*[9] report m. p. 120—122°, $[\alpha]_D$ +38°, $\nu_{max.}$ (in $CHCl_3$) 1720 cm.$^{-1}$.

4α-Ethylcholestan-3β-ol (XVI).—Reduction of the above saturated ketone (806 mg.) with lithium aluminium hydride (300 mg.) in ether gave, after chromatography on alumina (grade H; 10% deactivated) and recrystallisation from methanol, the alcohol (558 mg.) as needles, m. p. 146—147°, $[\alpha]_D$ +28° (*c* 1·39), $\nu_{max.}$ (in CS_2) 1034 cm.$^{-1}$ (β-OH) (Found: C, 83·2; H, 12·4. Calc. for $C_{29}H_{52}O$: C, 83·4; H, 12·5%). Djerassi *et al.*[9] record m. p. 141—143°, $[\alpha]_D$ +24°.

Action of Thionyl Chloride on 4α-Ethylcholestan-3β-ol.—4α-Ethylcholestan-3β-ol (286 mg.) in ether (10 ml.) was treated at −10° with thionyl chloride (42 mg.) and pyridine (55 mg.). After 1 hr. the precipitated pyridine hydrochloride was separated by filtration and washed with ether. Evaporation of the filtrate gave a solid which was heated for 1 hr. with thionyl chloride (42 mg.) and then crystallised twice from ethyl acetate, to give the *sulphite* (XV) (231 mg.) as needles, m. p. 172—173°, $[\alpha]_D$ 0° (*c* 1·35) (Found: C, 79·2; H, 11·9; S, 3·5. $C_{58}H_{102}O_3S$ requires C, 79·3; H, 11·6; S, 3·65%), $\nu_{max.}$ (in Nujol) 1205 cm.$^{-1}$ (sulphite).

Hydrolysis of the compound with aqueous mineral acid gave the original alcohol.

4α-Ethylcholestan-3β-yl Toluene-p-sulphonate (XVII).—A mixture of 4α-ethylcholestan-3β-ol (427 mg.), pyridine (5 ml.), and toluene-*p*-sulphonyl chloride (427 mg.) was kept at room temperature for 2 days. Addition of water (200 ml.) and ether extraction yielded the *toluene-p-sulphonate* which separated from ether–methanol as needles (445 mg.), m. p. 141—142°, $[\alpha]_D$ +30·5° (*c* 1·68) (Found: C, 75·7; H, 10·1; S, 5·7. $C_{36}H_{58}O_3S$ requires C, 75·8; H, 10·15; S, 5·6%), $\nu_{max.}$ (in Nujol) 1600 (aromatic), 1190, 1170 (sulphonate), 845, and 815 cm.$^{-1}$ (aromatic).

4α-Ethylcholestane (XVIII).—The above toluene-*p*-sulphonate (309 mg.) in tetrahydrofuran (50 ml.) was boiled under reflux for 4·5 hr. with lithium aluminium hydride (723 mg.). The mixture was worked up in the usual way, to yield an oil which was dissolved in light petroleum and filtered through alumina (grade O; 5% deactivated). The resulting *4α-ethylcholestane* (218 mg.) separated from ethyl acetate–methanol as colourless needles, m. p. 89—90°, $[\alpha]_D$ +4·5° (*c* 2·48) (Found: C, 86·95; H, 13·1. $C_{29}H_{52}$ requires C, 87·0; H, 13·0%).

[17] Jouanneteau and Mentzer, *Compt. rend.*, 1958, **246**, 2495.

4-Ethylcholest-4-ene (XIII).—4-Ethylcholest-4-en-3-one (413 mg.) in ether (30 ml.) was added to a mixture of lithium aluminium hydride (0·15 g.) and aluminium chloride (1·0 g.) in ether (30 ml.). The mixture was boiled for 1·75 hr. and worked up in the usual way. The resulting oil in light petroleum was put on alumina (grade H; 15 g.). Elution with light petroleum (60 ml.) gave a colourless oil (333 mg.) which, after several crystallisations from ethyl acetate–methanol, gave *4-ethylcholest-4-ene* (150 mg.) as needles, m. p. 49—50°, $[\alpha]_D$ +69° (*c* 1·36) (Found: C, 87·1; H, 12·7. $C_{29}H_{50}$ requires C, 87·45; H, 12·55%). The compound gave an intense yellow colour with tetranitromethane in chloroform.

4β-Ethylcholestane (XIV).—4-Ethylcholest-4-ene (198 mg.) was hydrogenated over Adams catalyst (199 mg.) at 20°/765 mm. in ether–acetic acid (1 : 3 v/v). Hydrogen uptake was complete after 15 min. Filtration and evaporation of the solvent yielded an oil which separated from ethyl acetate–methanol as needles (170 mg.), m. p. 73—76°. Filtration in light petroleum through alumina (grade H) and recrystallisation gave *4β-ethylcholestane*, m. p. 75—77°, $[\alpha]_D$ +31° (*c* 1·04) (Found: C, 86·75, 87·2; H, 13·3, 12·95. $C_{29}H_{52}$ requires C, 87·0; H, 13·0%). The compound gave a very slight yellow colour with tetranitromethane in chloroform.

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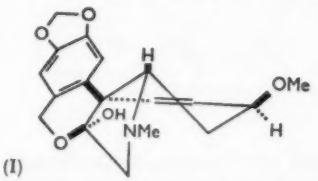
479. *Stereochemistry of the Hemiketal Moiety of Tazettine.*

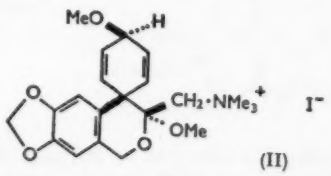
By YOSHISUKE TSUDA and SHOJIRO UYEO.

Treatment of *O*-methyltazettine methine methiodide with potassium t-butoxide leads, among other products, to two isomeric compounds (VII and VIII). Further examination of these yields results which establish the configuration of the hemiketal moiety of the parent alkaloid. Thus the absolute stereochemistry of tazettine is represented by formula (I).

THE structure of tazettine, including its absolute stereochemistry, has been established [1,2] with the exception of the configuration of the hemiketal moiety. Of the two possibilities, the *cis*-fused C/D ring system as in (I) (written in one of the two conformations of ring B) would be reasonable because of its greater stability. In the *trans*-fused case one might have thought that it should have isomerised upon treatment [1] with acid into the *cis*-form. In any event the hemiketal moiety in tazettine is stable, as shown [3] by its failure to react with carbonyl reagents. In the course of a restudy of the Hofmann degradation of *O*-methyltazettine methine methiodide (II) we have obtained compounds the further reactions of which are in complete agreement with the formula (I) for tazettine.



(I)

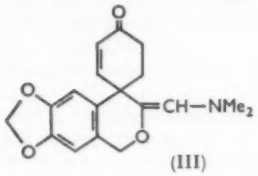


(II)

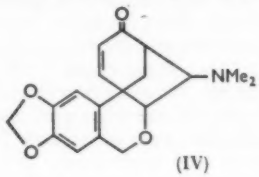
Vigorous treatment of *O*-methyltazettine methine methiodide [4] (II) with potassium t-butoxide in t-butyl alcohol furnished a complex mixture from which 2-*p*-methoxyphenyl-4,5-methylenedioxybenzyl alcohol, its acetate,[1] and five αβ-unsaturated ketones (compounds A—E) were isolated (see Experimental section). Three of these compounds, C, D, and E, have been shown to have the constitutions (III), (IV), and (V), respectively.[5]

[1] Ikeda, Taylor, Tsuda, Uyeo, and Yajima, *J.*, 1956, 4749.
[2] Irie, Tsuda, and Uyeo, *J.*, 1959, 1446.
[3] Ikeda, Taylor, and Uyeo, *Chem. and Ind.*, 1955, 1088.
[4] Kondo, Ikeda, and Okuda, *Ann. Report ITSUU Lab.*, 1950, **1**, 61.
[5] Tsuda and Uyeo, unpublished work.

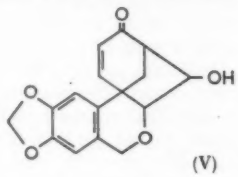
Compound A, $C_{19}H_{23}O_5N$, contained one methoxyl group and exhibited bands at 1660 (six-membered ring, conjugated ketone) and at 1408 cm.$^{-1}$ (methylene group adjacent to carbonyl) in the infrared spectrum and a strong absorption (ε 10,800 at 230 mμ) in the



(III)



(IV)

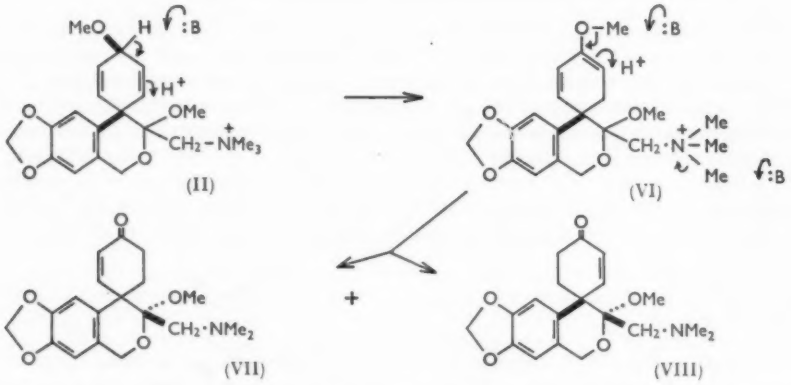


(V)

ultraviolet region which was unaffected by a change in pH. The nuclear magnetic resonance spectrum * exhibited singlets at 2·48, 1·99, 1·30, 0·09, and −1·26 p.p.m. indicative of NMe_2, $N{\cdot}CH_2{\cdot}\overset{|}{C}-$, OMe, $Ar{\cdot}CH_2{\cdot}O$, and methylenedioxy-groups. No peaks corresponding to $-O{\cdot}\overset{|}{C}H-$ were observed. Hydrogenation gave a dihydro-compound in which the double bond only had been saturated.

Compound B, $C_{19}H_{23}O_5N$, was apparently isomeric with compound A and readily distinguishable from it because it could not be obtained crystalline. Its close relation to compound A was established by hydrogenation, which gave the dihydro-derivative of compound A. Thus compounds A and B differed only in the position in the six-membered ring of the double bond conjugated to the carbonyl group.

We felt that compounds A and B should be the two possible products (VII and VIII) which could be formed from (II) as a result of elimination of one *N*-methyl group and prototropic rearrangement in ring B, followed by hydrolysis of the resulting enol ether (II ⟶ VI ⟶ VII and VIII).



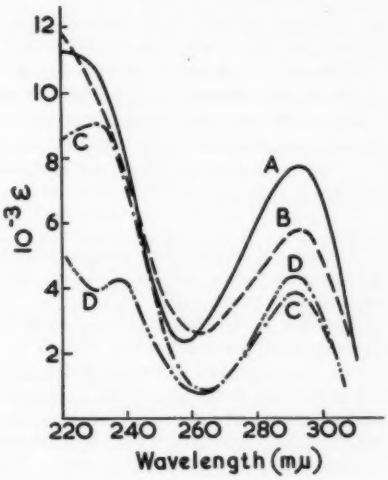
Compound B exhibited an infrared band at 1672 cm.$^{-1}$ (conjugated carbonyl) and also end-absorption (ε ~9900 at 230 mμ) in the ultraviolet spectrum, similar to that of compound A. However, upon acidification, this intensity, in contrast to that of compound A, was greatly diminished ($\lambda_{max.}$ 237 mμ, ε 4300; see Figure). This behaviour closely resembled that of dihydro-oxocrinine methine,[6] suggesting that a Michael type condensation takes place with compound B in acidic solution. In fact, the original isolation of compound B was possible only after its basified solution had been heated. To permit

* The nuclear magnetic resonance spectrum was taken for a 0·5 mol. chloroform solution on a Varian V4300, 40 mc. machine. Chemical shifts were measured relative to water (external standard).

[6] Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2567.

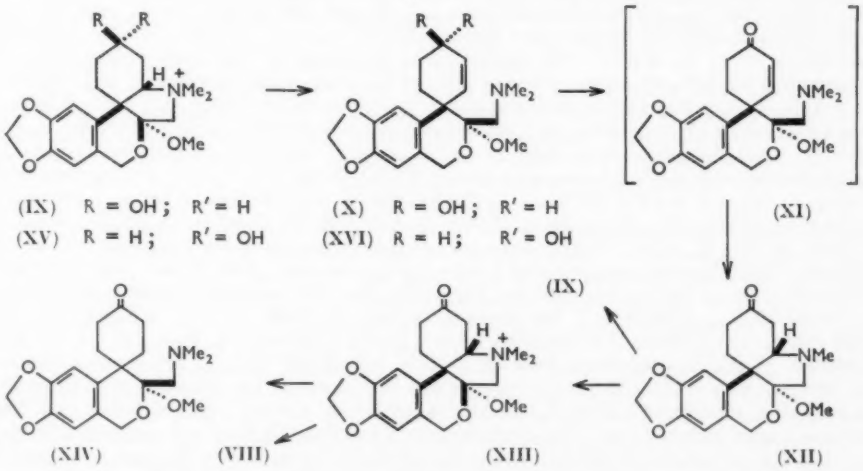
such a ready recyclisation, compound B, on the basis of formula (I) for tazettine, must be represented by (VIII) and thus compound A is (VII).

These structural assignments were proved by preparation of the dihydro-derivative of compound A by another route, and also by recyclisation of one of the intermediates where the position of the double bond (the same as in compound B) was certain. Methylation



Ultraviolet absorption of compound A in (A) EtOH *and* (C) *acidic* EtOH, *and of compound B in* (B) EtOH *and* (D) *acidic* EtOH.

of dihydrotazettinol [7] (or dihydroisotazettinol) [2] with dimethyl sulphate in aqueous potassium hydroxide gave the corresponding *O*-methyl quaternary salt (IX) characterised as the iodide. Hofmann degradation then gave a gummy methine (X) which on oxidation



with manganese dioxide in ether furnished the saturated ketone (XII), whose structure was confirmed by its borohydride reduction and subsequent quaternisation to regenerate the salt (IX). We had expected to get, by manganese dioxide oxidation, the unsaturated

[7] Tsuda and Uyeo, *J.*, 1961, 1055.

ketone (XI) but it had apparently recyclised with oxidative removal [2,8] of one of the *N*-methyl groups. In contrast, compound A (VII) was unaffected by manganese dioxide in ether, so that the ease of cyclisation must be a factor controlling the removal of one of the *N*-methyl groups.

Quaternisation of the ketone (XII ⟶ XIII), followed by hydrogenolysis over palladium–carbon in ethanolic sodium hydroxide, gave a methine (XIV) identical with the dihydro-derivative of compound A. Hofmann degradation of the quaternary ketone (XIII) gave, as expected, compound B (VIII).

The above results show that upon recyclisation the nitrogen goes back to its original point of attachment. Had the C/D ring system been *trans*-fused in tazettine recyclisation would have occurred, for steric reasons, on the side of ring B opposite to that of the parent compound. The validity of the above conclusions is unquestioned provided that we exclude an implausible inversion of the ketal stereochemistry during the *O*-methylation step.

Experimental

Ultraviolet absorption spectra were determined for 95% ethanol solutions, and infrared spectra were taken on Nujol mulls, unless otherwise stated. Light petroleum refers to the fraction of b. p. 50—70°.

Reaction of O-*Methyltazettine Methine Methiodide with Potassium t-Butoxide.*—*O*-Methyltazettine methine methiodide (II) (2 g.) and potassium t-butoxide (1 g.) in t-butyl alcohol (40 ml.) were heated under reflux for 10 hr., during which the methiodide gradually dissolved and potassium iodide separated. The solvent was evaporated under reduced pressure and the residue heated at 120—130°/0·5 mm. for 30 min. Water was added to the cooled mixture, and the whole was saturated with ammonium chloride and extracted with benzene which was washed with 5% hydrochloric acid. The benzene layer was dried (Na_2SO_4) and evaporated to dryness, to give a gum (0·35 g.) which was chromatographed in benzene over acid-washed alumina. Elution with benzene gave 2-*p*-methoxyphenyl-4,5-methylenedioxybenzyl acetate [1] (50 mg.), m. p. and mixed m. p. 87—89°. An ether eluate afforded 2-*p*-methoxy-4,5-methylenedioxybenzyl alcohol [1] (70 mg.), m. p. and mixed m. p. 147—149°. Further elution with chloroform and acetone gave *compound* E (V) (50 mg.) which crystallized as prisms (from chloroform), m. p. 239—240°, $[\alpha]_D$ ±0° (*c* 1·0 in acetone), $\lambda_{max.}$ 235 and 290 mμ (log ε 4·14 and 3·72), $\nu_{max.}$ 3390 (OH) and 1664 cm.$^{-1}$ (conjugated ketone) (Found: C, 66·9; H, 4·9; OMe, 0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). The acidic extract was basified with sodium carbonate and repeatedly extracted with ether. Concentration of the ether yielded *compound* C (III) (0·27 g.), m. p. 163—165° (yellow needles from methanol), $[\alpha]_D$ ±0° (*c* 0·5 in $CHCl_3$), $\lambda_{max.}$ 232 and 292 mμ (log ε 4·41 and 3·84), $\nu_{max.}$ 1670 cm.$^{-1}$ (conjugated ketone) (Found: C, 68·9; H, 5·9; N, 4·2; OMe, 0. $C_{18}H_{19}NO_4$ requires C, 69·0; H, 6·1; N, 4·5%). The mother-liquor was evaporated and triturated with methanol, to give *compound* D (IV) (40 mg.), m. p. 204—205° (prisms from methanol), $[\alpha]_D$ ±0° (*c* 0·8 in EtOH), $\lambda_{max.}$ 235 and 290 mμ (log ε 4·05 and 3·74), $\nu_{max.}$ 1672 cm.$^{-1}$ (conjugated ketone) (Found: C, 68·9; H, 6·1; N, 4·8; OMe, 0; *C*-Me, 0. $C_{18}H_{19}NO_4$ requires C, 69·0; H, 6·1; N, 4·5%). Chromatography of the mother-liquor from compounds C and D in benzene over alumina gave *compound* A (0·2 g.), m. p. 101—102° (VII) (prisms from methanol), $[\alpha]_D$ +46° (*c* 3·5 in $CHCl_3$), $\lambda_{max.}$ 292 mμ (log ε 3·89), and end-absorption at 220—230 mμ (log ε 4·05—4·03), $\nu_{max.}$ 2750 (NMe_2), 1660 (conjugated ketone), 1408 ($CO{\cdot}CH_2$) in Nujol mull, and 2736 (NMe_2) and 1669 cm.$^{-1}$ (conjugated ketone) in $CHCl_3$ (Found: C, 66·3; H, 6·5; N, 3·9; OMe, 9·0. $C_{19}H_{23}NO_5$ requires C, 66·1; H, 6·7; N, 4·1; 1OMe, 9·0%). The aqueous solution (*ca.* 200 ml.) from which the basic substances had been removed by extraction with ether was heated, after addition of sodium hydroxide (*ca.* 20 g.), on a water-bath for 5 min. and then extracted again with benzene. The benzene extract was dried (K_2CO_3) and evaporated to give an oil (0·1 g.) which was distilled at about 170° (bath)/0·1 mm. to give the pure *compound* B (VIII) as a colourless gum, $[\alpha]_D$ −238° (*c* 3·6 in $CHCl_3$), $\lambda_{max.}$ 292 mμ (log ε 3·76) and end-absorption at 220—230 mμ (log ε 4·07—4·0), $\nu_{max.}$ 2802 (NMe_2) and 1672 cm.$^{-1}$ (conjugated ketone) in $CHCl_3$. This compound is readily soluble in ether but changed in air into an ether-insoluble material.

Hydrogenation of Compound A.—Compound A (VII) (0·1 g.) in ethanol (10 ml.) was

[8] Henbest and Thomas, *J.*, 1957, 3032.

hydrogenated over 10% palladium–carbon (0·1 g.) for 1·5 hr. The filtered solution was evaporated and the residue crystallized from methanol to give *dihydro-compound* A (XIV) (80 mg.) as prisms, m. p. 97—98°, $[\alpha]_D$ −139° (*c* 0·8 in $CHCl_3$), $\lambda_{max.}$ 235 and 295 mμ (log ε 3·33 and 3·78), $\nu_{max.}$ 2760 (NMe_2), 1700 (C=O), 1403 ($CO{\cdot}CH_2$) in Nujol mull and 2765 (NMe_2) 1701 (C=O), 1404 cm.$^{-1}$ ($CO{\cdot}CH_2$) in $CHCl_3$ (Found: C, 66·0; H, 7·4. $C_{19}H_{25}NO_5$ requires C, 65·7; H, 7·3%).

Hydrogenation of Compound B.—Compound B (VIII) (0·15 g.) in ethanol (10 ml.) containing 10% ethanolic sodium hydroxide (2 ml.) was hydrogenated over 10% palladium–carbon for 1 hr. After removal of the catalyst the filtrate was diluted with water and extracted with ether which was re-extracted with 5% hydrochloric acid. Basification of the acidic solution with sodium carbonate and extraction with ether gave a gum after evaporation which was chromatographed over alumina. A dihydro-compound (XIV) (100 mg.), m. p. 96—97° (from ether–light petroleum), was isolated from benzene–ether eluates. The m. p. was not depressed on admixture with dihydro-compound A and the infrared spectra were identical.

Methylation of Dihydrotazettinol.—10% Aqueous potassium hydroxide (40 ml.) was added at a rate of 4 ml. an hour to a stirred mixture of dihydrotazettinol [7] (0·5 g.) and dimethyl sulphate (5 ml.). After an additional 2 hours' stirring, the mixture was neutralized with 20% sulphuric acid and was evaporated to dryness under reduced pressure after addition of potassium iodide (0·5 g.). The residue was repeatedly extracted with boiling chloroform, and the chloroform was dried (K_2CO_3) and evaporated to give *dihydro-O-methyltazettinol methiodide* (IX) (0·3 g.) as needles (from ethanol), m. p. 253—254° (decomp.) (Found: C, 47·9; H, 5·6. $C_{18}H_{22}NO_5,CH_3I$ requires C, 48·0; H, 5·5%).

Methylation of Dihydroisotazettinol.—Dihydroisotazettinol (0·2 g.) was methylated by the procedure described for dihydrotazettinol, to yield *dihydro-O-methylisotazettinol methiodide* (XV) (0·2 g.) as plates (from ethanol), m. p. 245—247° (decomp.) (Found: C, 48·2; H, 5·7%).

Hofmann Degradation of Dihydro-O-methyltazettinol Methiodide.—The methiodide (IX) (0·28 g.) and an excess of freshly prepared silver oxide in methanol (10 ml.) and water (10 ml.) were stirred for 30 min., then filtered, and the silver salts were washed with methanol and water. The combined filtrates and washings were evaporated to dryness and the residue was heated at 150—160°/0·5 mm. for 20 min. The resulting product was taken up in ether, which was washed with water, then concentrated to dryness to yield the gummy methine (X) (0·18 g.).

Hofmann Degradation of Dihydro-O-methylisotazettinol Methiodide.—The methiodide (XV) (0·5 g.) was subjected to the Hofmann degradation as described above to give the *methine* (XVI) (0·35 g.), m. p. 133—134°, (from ether–light petroleum), $[\alpha]_D$ −402° (*c* 2·9 in EtOH) (Found: C, 65·7; H, 7·2. $C_{19}H_{25}NO_5$ requires C, 65·7; H, 7·3%).

Dihydro-O-methyltazettinone (XII).—(*a*) The methine (X) (0·1 g.) in ether (10 ml.) was stirred with manganese dioxide (1 g.) for 1 hr. at room temperature. Manganese dioxide was removed and washed with ether, and the combined filtrates and washings were evaporated to give *dihydro-O-methyltazettinone* (XII) (90 mg.), m. p. 164—165° (needles from ethanol), $[\alpha]_D$ −131° (*c* 1·8 in $CHCl_3$), $\lambda_{max.}$ 237 and 294 mμ (log ε 3·66 and 3·71), $\nu_{max.}$ 1712 cm.$^{-1}$ (CO) (Found: C, 64·9; H, 6·2. $C_{18}H_{21}NO_5$ requires C, 65·2; H, 6·4%).

(*b*) The methine (XVI) (0·14 g.) in ether (14 ml.) was stirred with manganese dioxide (1·4 g.) for 18 hr. Chromatography of the resulting product in benzene over alumina furnished from a benzene eluate the starting material (50 mg.), m. p. and mixed m. p. 130—132°, and from benzene–chloroform eluate dihydro-*O*-methyltazettinone (XII) (40 mg.), m. p. 161—163°. No depression of m. p. was observed on admixture with the sample obtained as in (*a*). The infrared spectra of the two samples were identical.

Dihydro-O-methyltazettinol Methiodide (IX) *from Dihydro-O-methyltazettinone* (XII).—Dihydro-*O*-methyltazettinone (XII) (25 mg.) and sodium borohydride (50 mg.) in ethanol (5 ml.) were kept at room temperature for 12 hr. After removal of the ethanol, water was added and the mixture extracted with chloroform which was concentrated to dryness. The residue in methanol was heated under reflux with an excess of methyl iodide for 3 hr., the solvent was then removed, and the residue crystallized from ethanol to give dihydro-*O*-methyltazettinol methiodide (IX), m. p. and mixed m. p. 249—252° (decomp.). The infrared spectrum was identical with that of the specimen obtained as above.

Dihydro-O-methyltazettinone Methiodide (XIII).—Dihydro-*O*-methyltazettinone (XII) (200 mg.) and methyl iodide (2 ml.) in methanol (10 ml.) were refluxed for 6 hr. After removal of methanol, water was added, and the whole basified with a few drops of aqueous ammonia and

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extracted with ether which removed some unchanged starting material (90 mg.). The water layer was concentrated to dryness *in vacuo*, to yield the methiodide (XIII) as a gum.

Dihydro-compound A (XIV).—The above methiodide (XIII) (70 mg.) in 5% ethanolic sodium hydroxide (10 ml.) was hydrogenated over 10% palladium–carbon (100 mg.) at room temperature for 3 hr. After removal of the catalyst and concentration of the filtrate to dryness, water was added and the whole extracted with ether which was re-extracted with 2% hydrochloric acid. Basification of the acidic solution with sodium carbonate and extraction with ether afforded an oil which was chromatographed in benzene over alumina. Benzene and benzene–chloroform eluates were combined and rechromatographed in chloroform over silica gel. Elution with methanol–chloroform (1 : 99) gave dihydro-compound A (XIV) (30 mg.) as prisms, m. p. 96—98° after crystallization from ether–light petroleum. The m. p. was not depressed on admixture with the sample derived from compound A and the infrared spectra of the two samples were identical.

Compound B.—Dihydro-*O*-methyltazettinone methiodide (XIII) (50 mg.) and 20% aqueous sodium hydroxide (5 ml.) in water (5 ml.) and benzene (10 ml.) were heated on a water-bath for 5 min. The benzene layer was separated, dried (K_2CO_3), and evaporated to dryness, yielding compound B (VIII) as a gum whose infrared spectrum in chloroform was identical with that of compound B.

We are indebted to Dr. W. I. Taylor of CIBA Pharmaceutical Products, New Jersey, and Dr. W. C. Wildman of the National Heart Institute, National Institutes of Health, Maryland for valuable discussions.

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480. *Reactions of Uranium and Some Uranium Compounds with Nitrosyl Chloride, and with Liquid Nitrosyl Chloride–Dinitrogen Tetroxide Mixtures.*

By C. C. Addison and N. Hodge.

The paper deals with reactions in the system uranium–nitrosyl chloride–dinitrogen tetroxide. Uranium does not react with liquid dinitrogen tetroxide, but does react when nitrosyl chloride is added. Uranyl compounds are always formed in the presence of dinitrogen tetroxide. At all concentrations up to 85% of NOCl, the product is the addition compound $UO_2(NO_3)_2,N_2O_4$. At higher concentrations of nitrosyl chloride, a compound $UO_2Cl_2,NOCl$ is produced (which is the corresponding compound on the nitrosyl chloride solvent system), but nitrate is present in the product at all concentrations below 98% of NOCl. In pure nitrosyl chloride the uranium(IV) oxidation state is stable, and uranium reacts with the liquid to give UCl_4,xNOCl; x is usually ~2, but its variability suggests that 1 : 1 and 1 : 3 solvates may also exist. The nitrosyl chloride addition compounds have high thermal stability and are probably ionic complexes. These reactions of uranium metal are correlated by reference to the reactions of nitrosyl chloride with uranyl chloride, uranium tetra- and penta-chloride, the oxides UO_3 and U_3O_8, and uranyl nitrate–dinitrogen tetroxide, and to the solvolysis of uranium tetra- and penta-chloride by dinitrogen tetroxide.

Reactions involving non-aqueous inorganic solvents have usually been carried out in a single, pure solvent; by the use of mixed solvents, however, products can be varied by change in composition of the reaction medium.[1] Uranium does not react with dinitrogen tetroxide alone, but does react with liquid nitrosyl chloride and with mixtures of the two

[1] Addison, *Roy. Inst. Chem. Monograph* No. 2, 1960.

solvents. Each of the pure liquids undergoes self-ionisation ($NOCl \rightleftharpoons NO^+ + Cl^-$; $N_2O_4 \rightleftharpoons NO^+ + NO_3^-$) and thus represents a solvent system in its own right. In the mixture, the relative extent to which the two systems influence the reaction is revealed in the extent to which chlorides or nitrates appear in the products. A further feature of interest in the use of uranium arises from possible variations in its oxidation state; in dinitrogen tetroxide, uranium compounds tend to the U(VI) state, whereas the oxidising powers of nitrosyl chloride are much less pronounced.

The present paper gives a general review of reactions involving uranium metal, uranium halides, nitrosyl chloride, and dinitrogen tetroxide, and their interrelations. A more detailed study of the properties of individual compounds will be described in later papers.

Results and Discussion

Reactions in Nitrosyl Chloride.—(a) *Uranyl chloride.* On addition of liquid nitrosyl chloride, uranyl chloride was converted rapidly into the 1 : 1 addition compound $UO_2Cl_2,NOCl$, which remained as a pale yellow powder on evaporation of the excess of solvent at room temperature. It is stable at room temperature in the absence of moisture, and there was no evidence of compounds involving other molecular ratios. In contrast, uranyl chloride normally combines with metal chlorides and alkylammonium chlorides to yield tetrachlorodioxouranate salts $M_2[UO_2Cl_4]$ (where M is a univalent cation), and the formula $UO_2Cl_2,2X$ predominates for the many molecular addition complexes which uranyl chloride forms with organic compounds.[2] Uranyl chloride–nitrosyl chloride is readily soluble in nitromethane; on electrolysis of a 0·06M-solution the uranium concentration increased in the anode compartment, and nitric oxide was evolved at the cathode, so that the compound may be represented in the ionic form $(NO^+)[UO_2Cl_3]^-$. The insolubility of uranyl chloride–nitrosyl chloride in nitrosyl chloride may suggest a dinuclear structure; many established mononitrosyl compounds, *e.g.*, $FeCl_3,NOCl$, $AlCl_3,NOCl$, and $SbCl_5,NOCl$ are soluble, whereas dinitrosyl compounds are generally insoluble.[3]

Uranyl chloride–nitrosyl chloride has high thermal stability, and heating at 220—240° for 2 hr. at 0·2 mm. was necessary to remove all nitrosyl chloride; pure uranyl chloride remained.

(b) *Uranyl nitrate–dinitrogen tetroxide.* The compounds $UO_2Cl_2,NOCl$ and $UO_2(NO_3)_2,N_2O_4$ are corresponding compounds in the nitrosyl chloride and dinitrogen tetroxide solvent systems. The reaction

$$UO_2(NO_3)_2,N_2O_4 + 3NOCl \rightleftharpoons UO_2Cl_2,NOCl + 3N_2O_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

was examined, first, by addition of liquid nitrosyl chloride to uranyl nitrate–dinitrogen tetroxide. The mixture was kept at −7° for 6 hr., and the mixed solvents were then evaporated. After four successive treatments with nitrosyl chloride, approximately half of the uranyl nitrate was converted into chloride, and four further treatments were necessary for complete conversion. The equilibrium lies well to the left-hand side, since both uranyl chloride and uranyl chloride–nitrosyl chloride are converted completely into uranyl nitrate–dinitrogen tetroxide by a single treatment with liquid dinitrogen tetroxide.

(c) *Uranium tetrachloride and pentachloride.* These reactions were carried out primarily to determine the influence of nitrosyl chloride on the lower-valency states of uranium, and the products have been given preliminary examination only. The green tetrachloride underwent an immediate change, and after evaporation of the excess of liquid a bright orange powder remained, in which the uranium was still in the quadrivalent state (compare the behaviour of dinitrogen tetroxide discussed below). When this product was heated, nitrosyl chloride was evolved, but the orange compound has a high thermal stability,

[2] Katz and Robinowitch, "The Chemistry of Uranium," McGraw-Hill, New York, 1951, pp. 583, 584.

[3] Burg and McKenzie, *J. Amer. Chem. Soc.*, 1952, **74**, 3143.

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and heating at 240° for several hours under a vacuum was necessary to remove all the nitrosyl chloride. Most of the residue also sublimed at this temperature, condensing as green crystals of uranium tetrachloride, so that the orange product is an addition compound $UCl_4,xNOCl$. However, in contrast to the uranyl chloride addition compound, the value of x is not definite: in different preparations, it varied between 1·8 and 2·3. It is probable that the main product is $UCl_4,2NOCl$, but that less stable compounds having molecular ratios 1 : 1 and 1 : 3 are also formed. Vapour-pressure–composition data are being determined to define this system more precisely.

Uranium pentachloride reacted immediately on immersion, becoming orange-yellow. The increase in weight on evaporation of solvent at room temperature was 31·0% ($UCl_5 \longrightarrow UCl_5,2NOCl$ requires 31·5%). With ferric chloride and aluminium chloride, 2 : 1 as well as 1 : 1 addition compounds with nitrosyl chloride are known,[3] the additional molecule of nitrosyl chloride being combined with the NO^+ ion, *i.e.*, as $[NO^+,NOCl][FeCl_4^-]$. This formulation may also be applied to the compound $UCl_5,2NOCl$ to retain the maximum co-ordination number of 6 in the uranium chloro-complex. Like the uranyl chloride addition compound, the addition compounds with uranium tetra- and penta-chloride are probably ionic compounds $(NO^+)_2[UCl_6]^{2-}$ and $[NO^+,NOCl][UCl_6]^-$. However, on microscopic examination of the latter it appeared that both orange and yellow particles were present. Disproportionation to U(IV) and U(VI) may therefore have occurred, but in the direct reaction with uranium tetra- or penta-chloride there was no evidence that nitrosyl chloride acts as an oxidising agent.

(d) *Uranium oxides.* Uranium trioxide reacted slowly with liquid nitrosyl chloride. Complete reaction according to the equation $UO_3 + 3NOCl \longrightarrow UO_2Cl_2,NOCl + N_2O_3$ required 7 days' immersion in the liquid at −7°. The oxide U_3O_8 reacted even more slowly, and its reactivity depended to some extent on its method of preparation. The most active sample was prepared by heating ammonium diuranate to 650°; after immersion for 7 days at −7° in liquid nitrosyl chloride, 40 wt. % of the oxide had been converted into $UO_2Cl_2,NOCl$. Samples of the oxide obtained by heating ammonium diuranate to the more usual 900—1000° reacted much more slowly.

(e) *Uranium metal.* Nitrosyl chloride was condensed on to uranium metal at −70° and allowed to warm slowly. Reaction was slow below −40°, but the rate increased rapidly above this temperature; reaction was very vigorous at −20°, with evolution of nitric oxide. The controlled low-temperature reaction gave a bright orange, homogeneous powder; all the uranium was in the U(IV) oxidation state, and the product was identical with that formed by direct addition of uranium tetrachloride to nitrosyl chloride. The empirical formula of several such products was near $UCl_4,2{\cdot}3NOCl$, so that again the product probably consists of the disolvate $UCl_4,2NOCl$ together with the trisolvate $UCl_4,3NOCl$, having comparable stability and indistinguishable under the microscope. The reaction is considered to involve initial electron-transfer from uranium to the NO^+ ion (present as a result of self-ionisation of the liquid): $U + NO^+ \longrightarrow U^+ + NO$. This process will then continue stepwise until the uranium ion reaches the minimum oxidation state which is stable in nitrosyl chloride: $U + 4NO^+ \longrightarrow U^{4+} + 4NO$. During this reaction there was no evidence of the formation of products involving lower oxidation states of uranium.

When the reaction was allowed to proceed vigorously at about −20°, the product was a mixture of $UCl_4,xNOCl$ with the pale yellow uranyl compound $UO_2Cl_2,NOCl$. The production of the latter must be due to side reactions, probably involving the oxides of nitrogen which are produced copiously under these conditions. [Results given below indicate that any nitrogen dioxide present would immediately oxidise U(IV) to the uranyl compound.]

Dry gaseous nitrosyl chloride has little effect on a freshly filed uranium-metal surface at 100°, a faint stain appearing after prolonged treatment. However, if the nitrosyl chloride is not scrupulously dried, reaction is vigorous.

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Solvolysis by Dinitrogen Tetroxide.—Reactions of uranium halides in liquid dinitrogen tetroxide were studied to determine the extent to which any such halides initially produced in the mixed solvent nitrosyl chloride–dinitrogen tetroxide would be influenced by the presence of the tetroxide.

On immersion in the liquid tetroxide at 20°, uranium tetrachloride changed, first, to an orange compound [which may be the unstable $U(NO_3)_4$], then to the lemon-yellow $UO_2(NO_3)_2,N_2O_4$. Nitrosyl chloride was continuously evolved, and complete solvolysis

$$UCl_4 + 4N_2O_4 \longrightarrow UO(NO_3)_2,N_2O_4 + 4NOCl$$

required 36 hr. at 20°. The corresponding reaction

$$UCl_5 + 4N_2O_4 \longrightarrow UO_2(NO_3)_2,N_2O_4 + 4NOCl + \tfrac{1}{2}Cl_2$$

was complete in 20 hr. at 20°. Neither chloride is soluble in dinitrogen tetroxide, and the slowness of these solvolyses is largely due to this. When dinitrogen tetroxide is added to a solution of either chloride in nitromethane, the reaction is complete within 30 min. at 20°. The rapid conversion of uranyl chloride–nitrosyl chloride into uranyl nitrate–dinitrogen tetroxide has been referred to above (equation 1); uranyl chloride behaves similarly.

In the presence of dinitrogen tetroxide, uranium(IV) and uranium(V) are therefore oxidised to the uranium(VI) state, and solvolysis of the higher uranium chlorides is a fairly ready process. The influence which a particular metal, its valency state, and the covalent character of its chloride have on the extent to which solvolysis occurs is not yet understood. Zinc chloride,[4] the titanium and zirconium halides,[5] and the alkylammonium halides [6] are readily solvolysed, whereas the anhydrous chlorides AgCl, NaCl, KCl, $FeCl_3$, and $CrCl_3$ do not react with pure dinitrogen tetroxide.

Reaction of Uranium Metal with Nitrosyl Chloride–Dinitrogen Tetroxide Mixtures.—Our interest in these mixtures arises from the fact that, although dinitrogen tetroxide is a relatively unreactive liquid, its reactivity can be stimulated by mixing with other liquids, *e.g.*, inert organic solvents such as nitromethane,[7] organic donor solvents,[7] and dinitrogen trioxide.[8] Such mixtures retain all the essential features of the dinitrogen tetroxide solvent system, apart from solubility properties and reactivity. Nitrosyl chloride is also a suitable additive, and mixtures are readily prepared by passage of the tetroxide vapour through (say) calcium chloride. Experiments were therefore conducted to determine the composition ranges over which the products of reaction with uranium remained characteristic of the N_2O_4 system, and the results are summarised in Table 1.

TABLE 1. *Products of reaction of uranium with* N_2O_4–NOCl *mixtures.*

NOCl (wt. %)	Reaction product after removal of solvents at room temp.
0	No reaction with uranium
All concns. up to 84%	$UO_2(NO_3)_2,N_2O_4$
84—98	Mixture of $UO_2(NO_3)_2,N_2O_4$ and UO_2Cl_2,NOCl, the proportion of the latter increasing with NOCl concn.
99	Mixture of UO_2Cl_2,NOCl and UCl_4,xNOCl
100	UCl_4,xNOCl

The striking feature is that the nitrosyl chloride concentration can be increased to 84% before any chloride appears in the product. In view of the reactions discussed earlier, and the absence of reaction between uranium and the pure tetroxide, the reaction mechanism

[4] Addison and Lewis, *J.*, 1951, 2843.
[5] Gutmann and Tannenberger, *Monatsh.*, 1956, **87**, 421.
[6] Addison, Conduit, and Thompson, *J.*, 1951, 1298.
[7] Addison, Sheldon, and Hodge, *J.*, 1956, 3900.
[8] Addison, Lewis, and Thompson, *J.*, 1951, 2838.

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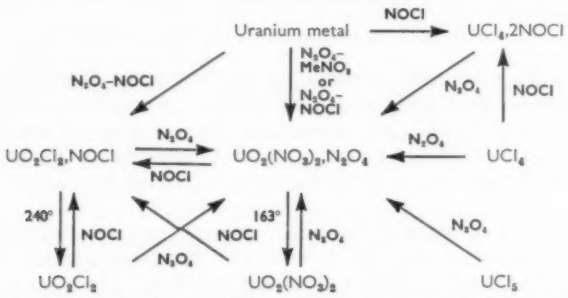
must involve initial attack by nitrosyl chloride, followed by oxidation and solvolysis of the chloride by dinitrogen tetroxide:

$$U + 6NOCl \longrightarrow UCl_4,2NOCl + 4NO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$
$$UCl_4,2NOCl + N_2O_4 \longrightarrow UO_2Cl_2,NOCl + 3NOCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$
$$UO_2Cl_2,NOCl + 3N_2O_4 \longrightarrow UO_2(NO_3)_2,N_2O_4 + 3NOCl \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

If the product is isolated at an early stage in the reaction, it is seen to consist of the yellow uranyl nitrate–dinitrogen tetroxide contaminated by a bright orange compound. The latter contains uranium in an oxidation state lower than U(VI), and is probably the uranium tetrachloride–nitrosyl chloride addition compound.



From the experiments with dilute solutions of dinitrogen tetroxide in nitrosyl chloride, it is clear that the presence of any tetroxide in the liquid mixture results in ultimate oxidation of U(IV) to U(VI). With 1% of tetroxide, appreciable oxidation to uranyl chloride occurs, and with mixtures containing 2% of tetroxide no uranium tetrachloride remains in the product.

The reactions of dinitrogen tetroxide and nitrosyl chloride with uranium, and the interconversion of nitrates and chlorides, are summarised in the annexed scheme.

Experimental

The preparation of dinitrogen tetroxide and nitrosyl chloride, the preparation of the mixtures, and their analysis were carried out as already described.[9]

Uranyl Chloride.—Passage of hydrogen chloride gas over the hydrate for 24 hr. at 300° gave anhydrous uranyl chloride as a yellow powder (Found: U, 69·7. Calc. for UO_2Cl_2: 69·8%).

Analysis of Uranyl Chloride–Nitrosyl Chloride.—Both acid and alkaline hydrolysis were employed. A weighed sample was sealed in a thin-walled phial, which was broken by being shaken in a bottle containing 0·1N-hydrochloric acid. The temperature was kept at 0° to reduce the vigour of the hydrolysis. Chlorine was determined as silver chloride. Uranium was precipitated as ammonium diuranate by addition of carbonate-free ammonia, and the precipitate was ignited at 900° to the oxide U_3O_8. In the alkaline hydrolysis, 2N-sodium hydroxide at 0° was used. Nitrogen was determined separately after alkaline hydrolysis in 5N-sodium hydroxide. Under these conditions, nitrogen contents obtained by the Kjeldahl method, and by determining nitrite by potassium permanganate titration, were in agreement. When hydrolysis was carried out in sodium hydroxide solutions more dilute than 5N, nitrite analyses were less satisfactory. Two alternative reactions are possible: [10]

$$NOCl + 2NaOH = NaNO_2 + NaCl + H_2O$$
$$3NOCl + 4NaOH = 3NaCl + NaNO_3 + 2NO + 2H_2O$$

but the second reaction is not significant at higher alkali concentrations. The product from the reaction of uranyl chloride with nitrosyl chloride reaction gave: N, 3·45%; on acid hydrolysis, U, 58·4; Cl, 26·8%; on alkaline hydrolysis, U, 58·4; Cl, 26·6% (Calc.

[9] Addison and Thompson, *J.*, 1949, S218.
[10] Perret and Perrot, *Compt. rend.*, 1931, **193**, 937.

for UO_2Cl_2,NOCl: U, 58·5; Cl, 26·2; N, 3·45%). In removing the last traces of excess of nitrosyl chloride from the addition compound, we were anxious that the latter should not be decomposed, and the slightly high chlorine content probably represents nitrosyl chloride adsorbed on the powder.

During thermal decomposition of uranyl chloride–nitrosyl chloride, the evolved gas was absorbed in a sodium hydroxide–calcium oxide tube, and its chloride content determined; the weight of evolved gas was determined directly from loss in weight of the addition compound. The residue gave: U, 69·5; Cl, 20·6% (Calc. for UO_2Cl_2: U, 69·8; Cl, 20·8%). In the evolved gas, Cl = 54·8% (Calc. for NOCl: 54·2%).

Uranyl Nitrate–Dinitrogen Tetroxide.—Such material was obtained by reaction of uranium metal (or the oxide UO_3 or U_3O_8) with mixtures of nitromethane and dinitrogen tetroxide. It is normally obtained as a yellow powder [11] but from solutions rich in nitromethane it can be crystallised as large (1 cm.) yellow crystals. Removal of dinitrogen tetroxide to leave the pure anhydrous nitrate can only be carried out under special conditions, which are not appropriate for analysis, and reaction products believed to consist of this compound (see Table 3) were analysed by hydrolysis in 2N-sodium hydroxide. After filtration of the uranate, total nitrogen was determined in the filtrate by the Kjeldahl method, and nitrite by titration with potassium permanganate solution. The uranate was dissolved in acid, reprecipitated as ammonium diuranate, and ignited to U_3O_8.

Uranium Chlorides.—These were prepared by passing an excess of dry chlorine over a mixture of the oxide U_3O_8 and carbon in a silica tube at 600°. The pentachloride and tetrachloride condensed as separate bands in the cool parts of the tube, the pentachloride predominating. For analysis, the latter was dissolved in water at 0° and oxidised by nitrous acid, and uranium and chloride were determined as U_3O_8 and AgCl respectively (Found: U, 57·4; Cl, 42·1. Calc. for UCl_5: U, 57·3; Cl, 42·6%). The tetrachloride was prepared by heating the pentachloride at 200° in a current of dry carbon dioxide, followed by sublimation at 600—650°. The product was dissolved in dilute sulphuric acid, and uranium determined by titration with potassium permanganate (Found: U, 62·5; Cl, 38·0. Calc. for UCl_4: U, 62·7; Cl, 37·3%).

When the addition compounds with nitrosyl chloride were dissolved in water or dilute acids, the uranium was oxidised to the U(VI) state by the nitrous acid produced, and these solutions could not be used for analysis. The nitrosyl chloride was therefore removed from the addition compound by heating under a vacuum, and the remaining chloride determined as stated above.

Metallic Uranium–Nitrosyl Chloride Reaction.—Relevant analyses are given in Table 2.

TABLE 2. *Products of reaction of uranium with nitrosyl chloride.**

Prepn. no.	Temp. of liquid NOCl	NOCl (%) in product	Analysis (%) of product after removal of NOCl at 240°		
			U(IV)	UO_2^{2+}	Cl
1	Below −40°	28·9	62·8	0	35·0
2	−30 to −20°	31·8	49·3	13·6	—
3	−30 to −20°	30·4	37·2	23·0	—

* UCl_4,2NOCl and UCl_4,3NOCl require 25·6 and 34·1% of NOCl, respectively.

In preparation 1, almost all of the product obtained after removal of nitrosyl chloride could be sublimed as the green tetrachloride. A trace of uranium(IV) oxide dichloride, $UOCl_2$, remained as unsublimable residue, and accounts for the somewhat low chlorine content. Under conditions of more vigorous reaction (preparations nos. 2 and 3) the quantity of uranyl compound produced was variable, though it appeared to increase with vigour of reaction. The evolved gases were passed through activated alumina, which absorbs nitrosyl chloride and any nitrogen dioxide; nitric oxide is not absorbed and was recognised by the formation of brown fumes in contact with atmosphere.

Reaction of Uranium with N_2O_4–NOCl *Mixtures.*—In all experiments, the liquid mixture was present in large excess. Over the 0—40% NOCl range, reaction was very slow. For example, freshly filed uranium metal was held in a sealed tube at 20° with a mixture containing 37% of nitrosyl chloride; a thin film of product developed after 24 hr. Reaction became more

[11] Gibson and Katz, *J. Amer. Chem. Soc.*, 1951, **73**, 5436.

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vigorous at concentrations above 40% of nitrosyl chloride. Analyses of products obtained at some higher concentrations are given in Table 3.

TABLE 3. *Reaction of uranium with* N_2O_4–NOCl *mixtures.*

Expt. no.	NOCl (wt. %)	Temp. of reaction mixture	Analysis (%) of product U(VI)	N_2O_4	Cl
1	70·0	−8°	50·0	18·7	0
2	84·1	−9	49·4	18·3	Trace
3	96·4	−22	53·2	—	22·0
4	97·8	−35	56·7	Trace	26·0
	$UO_2(NO_3)_2,N_2O_4$ requires		49·0	18·9	0
	$UO_2Cl_2,NOCl$ requires		58·5	0	26·2

In none of these experiments was uranium(IV) detected in the final product. With 70·0% and 84·1% of nitrosyl chloride, analysis shows the product to be $UO_2(NO_3)_2,N_2O_4$. This is one of the most stable of the metal nitrate–dinitrogen tetroxide addition compounds, but unless isolated with great care it readily loses a small amount of dinitrogen tetroxide. This is reflected in the slightly high uranium, and slightly low N_2O_4, analyses in expt. nos. 1 and 2. Over the narrow concentration range 84—97·8% of nitrosyl chloride, the product changes to uranyl chloride–nitrosyl chloride (expt. no. 4). At higher concentrations (about 99%) no trace of nitrate is found in the product (*i.e.*, no brown fumes are given off on ignition) but uranium(IV) chloride occurs in the product. This is recognised by sublimation, and by titration of an aqueous solution of the product after removal of nitrosyl chloride under a vacuum.

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481. *The Preparation of Complex Fluorides by Use of Sulphur Tetrafluoride as Fluorinating Agent.*

By R. D. W. KEMMITT and D. W. A. SHARP.

Sulphur tetrafluoride converts mixtures of alkali-metal fluorides and metal oxides, sulphides, and carbonyls into complex fluorides. Silver, thallous, and ammonium salts can also be prepared by use of this reagent.

RECENT work [1] has shown that sulphur tetrafluoride is a versatile fluorinating agent for the preparation of binary fluorides from inorganic oxides and sulphides. It has now been found that by using this reagent it is possible to prepare alkali-metal, ammonium, thallous, and silver(I) fluoroborates, hexafluorosilicates, hexafluorogermanates, hexafluorophosphates, hexafluoroarsenates, hexafluoroantimonates, hexafluorotitanates, hexafluoroniobates, hexafluorotantalates, hexafluoromolybdates(V), hexafluorotungstates(V), and hexafluorouranates(IV) (see Table). Sulphur tetrafluoride is a particularly convenient reagent since the other product from the reaction with oxides is thionyl fluoride which is volatile, and there is no solvolysis such as occurs when other non-aqueous fluorinating solvents (bromine trifluoride, iodine pentafluoride, selenium tetrafluoride, etc.) are used. Sulphur tetrafluoride also has the advantages that it may be prepared without the use of elementary fluorine [2] and that the reactants are not necessarily oxidised to the maximum valency state.

Sulphur tetrafluoride is a Lewis base and forms many adducts with other fluorides.[1,3] In the present work it has been found that previously unreported adducts are formed with niobium, tantalum, and molybdenum pentafluorides but, apart from molybdenum pentafluoride where a very approximately 1 : 1 adduct is formed, the stoicheiometries of the adducts do not correspond to a simple ratio between the Lewis acid and the Lewis base.

[1] Oppegard, Smith, Muetterties, and Engelhardt, *J. Amer. Chem. Soc.*, 1960, **82**, 3835.
[2] Tullock, Fawcett, Smith, and Coffman, *J. Amer. Chem. Soc.*, 1960, **82**, 539.
[3] Seel and Detmer, *Z. anorg. Chem.*, 1959, **301**, 113.

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Reactants	Reaction temp.	Solid products	Analysis (%) Found	Calc.		*X*-Ray data (Å) *
$2KF : 1B_2O_3$	200°	KBF_4	BF_4, 68·1	BF_4, 69·0	O,[a]	$a = 7{\cdot}84$, $b = 5{\cdot}68$, $c = 7{\cdot}37$
$2AgF : 1B_2O_3$	175	$AgBF_4$	Ag, 54·5	Ag, 55·4	O,[b]	$a = 7{\cdot}75$, $b = 5{\cdot}54$, $c = 7{\cdot}16$
$2NH_4F : 1B_2O_3$	180	NH_4BF_4	BF_4, 83·6	BF_4, 82·8	O,[c,d]	$a = 8{\cdot}89$, $b = 5{\cdot}68$, $c = 7{\cdot}21$
$2NaF : 1SiO_2$	350	Na_2SiF_6	Si, 14·0	Si, 14·8	H,[e]	$a = 8{\cdot}86$, $c = 5{\cdot}02$
$2NaF : 1GeO_2$	350	Na_2GeF_6	Ge, 30·1	Ge, 31·2	H,[e]	$a = 9{\cdot}10$, $c = 5{\cdot}13$
$2NaF : 1P_2S_5$	350	$NaPF_6$,S			N,[f,g]	$a = 7{\cdot}60$
$2KF : 1As_2O_3$	350	$KAsF_6$	As, 33·8	As, 32·9	R,[f]	$a = 4{\cdot}92$, $\alpha = 97{\cdot}2$
$2NaF : 1Sb_2O_3$	350	$NaSbF_6$	Sb, 46·3	Sb, 47·1	N,[h]	$a = 8{\cdot}18$
$2NaF : 1TiO_2$	350	Na_2TiF_6	Ti, 22·9	Ti, 23·1	H,[e]	$a = 9{\cdot}21$, $c = 5{\cdot}15$
$2NaF : 1Nb_2O_5$	350	$NaNbF_6$	Nb, 39·8	Nb, 40·4	N,[f]	$a = 8{\cdot}27$
$2NaF : 1Ta_2O_5$	350	$NaTaF_6$	Ta, 56·1	Ta, 56·9	N,[f]	$a = 8{\cdot}26$
$1LiF : 1Mo(CO)_6$	165	$LiMoF_6$	Mo, 44·5	Mo, 44·2	R,[i]	$a = 5{\cdot}44$, $\alpha = 57{\cdot}0°$
$2NaF : 1Mo(CO)_6$	200	$NaMoF_6$,NaF	Mo, 34·1	Mo, 34·9	N,[j]	$a = 8{\cdot}19$
$2NaF : 1MoO_2$	250	$NaMoF_6$,NaF			N,[j]	$a = 8{\cdot}20$
$2NaF : 1MoS_2$	400	$NaMoF_6$,NaF, MoS_2, S			N,[j]	$a = 8{\cdot}19$
$1CsF : 1Mo(CO)_6$	200	$CsMoF_6$	Mo, 29·5	Mo, 28·0	R,[j]	$a = 5{\cdot}29$, $\alpha = 96{\cdot}0°$
$1TlF : 1Mo(CO)_6$	165	$TlMoF_6$	Mo, 24·0	Mo, 23·2	R,[i]	$a = 5{\cdot}12$, $\alpha = 96{\cdot}6°$
$2NaF : 1W(CO)_6$	200	$NaWF_6$,NaF	M, 50·1	W, 50·7	N,[i]	$a = 8{\cdot}18$
$1CsF : 1W(CO)_6$	200	$CsWF_6$	W, 41·9	W, 42·7	R,[j]	$a = 5{\cdot}31$, $\alpha = 95{\cdot}5°$
$2NaF : 1UO_2$	350	Na_2UF_6	U, 60·1	U, 59·8	Several phases present	
Nb_2O_5	350	NbF_5,0·54SF_4	Nb, 37·8	Nb, 37·8		
Ta_2O_5	350	TaF_5,0·39SF_4	Ta, 56·8	Ta, 56·8		
$Mo(CO)_6$	165	MoF_5,0·69SF_4	Mo, 36·1	Mo, 36·1		

[a] Pesce, *Gazzetta*, 1930, **60**, 936. [b] Sharp and Sharpe, *J.*, 1956, 1855. [c] Hoard and Blair, *J. Amer. Chem. Soc.*, 1935, **57**, 1985. [d] Klinkenberg and Ketelaar, *Rec. Trav. chim.*, 1935, **54**, 959. [e] Cox, *J.*, 1954, 3251. [f] Cox, *J.*, 1956, 876. [g] Bode and Teufer, *Z. anorg. Chem.*, 1952, **268**, 20. [h] Schrewelius, *Z. anorg. Chem.*, 1938, **238**, 241. [i] Kemmitt and Sharp, unpublished results. [j] Hargreaves and Peacock, *J.*, 1957, 4212.

* Structure type is indicated by: H (hexagonal), O (orthorhombic), N (NaCl) and R (rhombohedral).

All sulphur tetrafluoride adducts are unstable in the presence of basic fluorides: the fluoride ion is a better Lewis base than sulphur tetrafluoride. The decomposition of SF_4,BF_3 with potassium fluoride has been suggested as a method of preparing pure sulphur tetrafluoride.[3]

Most of the complexes resulting from these reactions contain elements in the same valency state as the starting materials. However, fluorination of a mixture of alkali fluoride and molybdenum hexacarbonyl, molybdenum dioxide, or molybdenum disulphide gives molybdenum(v) complexes. It has previously been reported [1] that fluorination of molybdenum disulphide gives molybdenum tetrafluoride which was characterised as its dimethyl sulphoxide adduct. We suggest that the actual product from the fluorination of molybdenum disulphide is MoF_5,SF_4 (molybdenum tetrafluoride would most probably form a 1 : 2 adduct with sulphur tetrafluoride) and that this dissociates and disproportionates to MoF_4 and MoF_6 in solution with dimethylsulphoxide. Similar disproportionation occurs when molybdenum pentachloride forms complexes with oxygen-containing ligands.[4] The action of sulphur tetrafluoride on a mixture of alkali fluoride and tungsten hexacarbonyl also gives quinquevalent complexes.

Experimental

Alkali fluorides were dried by heating them in a platinum crucible. Thallous fluoride was prepared from thallous carbonate and hydrofluoric acid; silver(I) fluoride was prepared by the method of Andersen, Bak, and Hillebert.[5] "AnalaR" ammonium fluoride was used as supplied. Metal oxides were dried at 130° and molybdenum and tungsten carbonyls were resublimed before use. Sulphur tetrafluoride was used directly from cylinders of the gas, which were kindly supplied by E.I. du Pont de Nemours and Co. Inc. and Imperial Chemical Industries Limited.

[4] Gunduz and Sharp, unpublished observations.
[5] Andersen, Bak, and Hillebert, *Acta Chem. Scand.*, 1953, **7**, 236.

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Alkali fluoride–metal oxide, sulphide, or carbonyl mixtures in various ratios (see Table) were fluorinated with an excess of sulphur tetrafluoride at autogenous pressures in a stainless-steel bomb which was rocked and heated overnight. The gaseous products were pumped off and the solid complexes were subsequently handled in the dry box. All solid products were analysed (see Table). *X*-Ray powder photographs of samples sealed in Lindemann glass capillaries were taken with Cu-K_α or Co radiation; measured values of $\sin^2\theta$ were compared with values obtained from lattice constants recorded in the literature.

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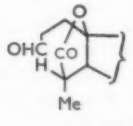
482. *Gibberellic Acid. Part XVIII.* Some Rearrangements of Ring* A.

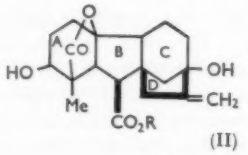
By B. E. CROSS, JOHN FREDERICK GROVE, and A. MORRISON.

Evidence is presented for the alkali-induced epimerisation of a 2-hydroxy-substituent in gibbane 1 ⟶ 4a-lactones. Under identical conditions gibb-3-ene 1 ⟶ 4a-lactones are rearranged to gibb-4-ene 1 ⟶ 3-lactones without epimerisation of a 2-hydroxyl substituent. Some degradations of the gibb-4-ene 1 ⟶ 3-lactone system are described and compared with similar degradations of the corresponding gibb-3-ene 1 ⟶ 4a-lactones.

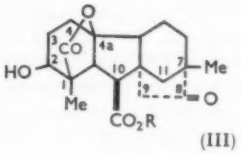
2(*ax*)-HYDROXYGIBBANE 1 ⟶ 4a-LACTONES † are epimerised [3,4] in dilute aqueous alkali to the more stable 2(*eq*)-epimers, and the evidence for the quasiaxial configuration of the 2-hydroxyl substituent in gibberellic acid has already been reported briefly.[3,4] A retro-aldol mechanism for the epimerisation *via* the intermediate (I) has been suggested.[5]



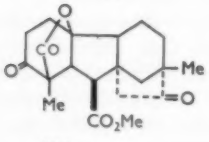
(I)



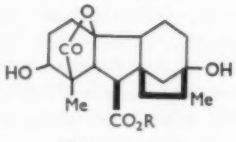
(II)



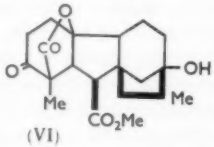
(III)



(IV)



(V)



(VI)

With 0·01N-sodium hydroxide at room temperature, gibberellin A_1 methyl ester † (II; R = Me) gave a mixture of the 2-hydroxy-epimers, which was separated into its

* Part XVII, *J.*, 1960, 3049.

† For nomenclature see Part XII.[1] In this and subsequent publications α and β are used to indicate the absolute configuration of substituents attached to the gibbane ring system and are no longer used to differentiate stereoisomeric reduction products [2] of gibberellic acid. The name "α-dihydrogibberellic acid" [2] for (II; R = H) is withdrawn in favour of the trivial name gibberellin A_1.

[1] Grove and Mulholland, *J.*, 1960, 3007.
[2] Grove, Jeffs, and Mulholland, *J.*, 1958, 1236.
[3] Cross, Grove, MacMillan, Mulholland, and Sheppard, *Proc. Chem. Soc.*, 1958, 221.
[4] Cross, Grove, MacMillan, Moffatt, Mulholland, Seaton, and Sheppard, *Proc. Chem. Soc.*, 1959, 302.
[5] Cornforth, personal communication; *Chem. and Ind.*, 1959, 184.

XUM

components by chromatography on alumina. With a reaction time of 6 hr. the ratio equatorial : axial epimer recovered was approximately 2·5 : 1, but the simultaneous hydrolysis of the ester grouping rapidly reduced the total yield of neutral material and a detailed study of the course of the epimerisation was not attempted.

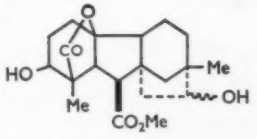
The 2(*eq*)-hydroxy-epimer (II; R = Me), m. p. 193°, underwent rearrangement of rings C/D [6] with dilute mineral acid and afforded the 2(*eq*)-hydroxy-8-keto-acid (III; R = H) and its methyl ester (III; R = Me). Oxidation of the latter by chromic oxide gave the same 2,8-diketo-ester (IV) as was obtained by oxidation of the 2(*ax*)-hydroxy-8-keto-ester (III; R = Me), derived previously [7] by acid-induced rearrangement of gibberellin A_1 methyl ester. The 2(*ax*)-hydroxy-8-keto-acid (III; R = H) was isomerised by 0·1N-sodium hydroxide to the 2(*eq*)-hydroxy-epimer. Similarly, with dilute alkali, methyl tetrahydrogibberellate [7] (V; R = Me) and methyl 8-epitetrahydrogibberellate [7] gave the corresponding 2(*eq*)-hydroxy-compounds, m. p. 235—239° and 166—168°, respectively. Both compounds were also obtained by catalytic reduction of the 2(*eq*)-hydroxy-epimer of gibberellin A_1 methyl ester followed by chromatography on alumina: separation of the 8-epimers by fractional crystallisation was not possible. Oxidation of methyl tetrahydrogibberellate and its 2(*eq*)-hydroxy-epimer by chromic oxide gave the same 2-ketone (VI), m. p. 161—163°: [7] the 8-epi-2-ketone [7] (VI), m. p. 131—133°, was obtained by oxidation of methyl 8-epitetrahydrogibberellate and its 2(*eq*)-hydroxy-epimer.

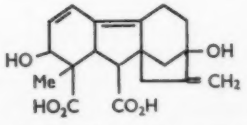
Alkaline hydrolysis of the 2(*eq*)-hydroxy-epimer (II; R = Me) gave the corresponding acid (II; R = H), identical with the pseudogibberellin A_1 of Takahashi *et al.*[8] since the dihydro-acid (V; R = H) (mixture of 8-epimers), obtained by catalytic reduction, was identical with an authentic specimen (for which we are indebted to Professor Y. Sumiki, University of Tokyo) of dihydropseudogibberellin A_1. The dihydro-acid (V; R = H) was shown to be a mixture of 8-epimers since methylation afforded a mixture of the 2(*eq*)-hydroxy-esters (V; R = Me). Isogibberellin A_1 obtained by Takahashi *et al.*[9] both by the action of alkali on the 2(*ax*)-hydroxy-8-keto-acid (III; R = H) (gibberellin C) and by acid treatment of pseudogibberellin A_1 is therefore the 2(*eq*)-hydroxy-epimer (III; R = H).

Reduction of the 2(*ax*)-hydroxy-keto-ester (III; R = Me) by sodium borohydride was stereospecific and afforded the 2(*ax*),8ξ-dihydroxy-ester (VII) which gave the 2,8-diketo-ester (IV) on oxidation by chromic oxide.

Reduction of the 2-ketone (VI), m. p. 161—163°, with sodium borohydride gave predominantly the 2(*eq*)-hydroxy-ester (V; R = Me), m. p. 235—239°, although about 10% of the 2(*ax*)-hydroxy-epimer was also formed. Some support for the retroaldol mechanism for the epimerisation of 2-hydroxygibbane 1 ⟶ 4a-lactones and for the existence of an equilibrium between the epimers in aqueous solution may be derived from the isolation of about 10% of the 2(*ax*)-hydroxy-ester (II; R = Me) when the 2(*eq*)-hydroxy-epimer, m. p. 193°, was shaken with 0·01N-sodium hydroxide.

(VII)





(VIII)

Gibberellenic acid [10] (VIII) was stable to alkali. This observation cannot be taken as indicating that the presence of a 1 ⟶ 4a-lactone bridge is essential for epimerisation since in the formation of gibberellenic acid movement of the double bond which finally appears in the 4a(4b)-position may enable the 2-hydroxy-group to become quasiequatorial.

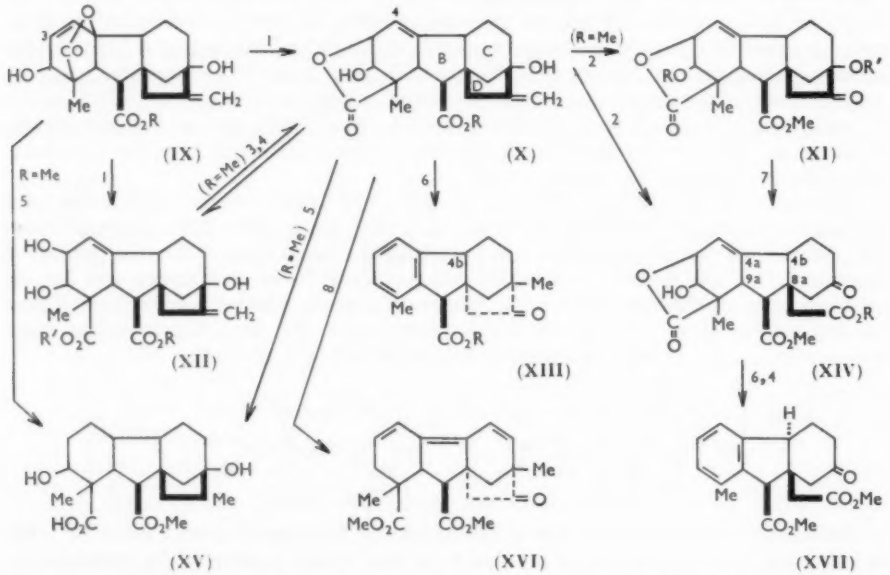
[6] Grove, MacMillan, Mulholland, and Turner, *J.*, 1960, 3049.
[7] Cross, *J.*, 1960, 3022.
[8] Takahashi, Kitamura, Kawarada, Seta, Takai, Tamura, and Sumiki, *Bull. Agric. Chem. Soc. Japan*, 1955, **19**, 267.
[9] Takahashi, Seta, Kitamura, Kawarada, and Sumiki, *Bull. Agric. Chem. Soc. Japan*, 1957, **21**, 75.
[10] Moffatt, *J.*, 1960, 3045.

XUM

The easy alkali-induced epimerisation of a 2-hydroxyl substituent in gibbane 1 ⟶ 4a-lactones is replaced in gibb-3-ene 1 ⟶ 4a-lactones by an allylic-type rearrangement to gibb-4-ene 1 ⟶ 3-lactones without concomitant epimerisation of the 2-hydroxyl substituent. With 0·01N-sodium hydroxide methyl gibberellate (IX; R = Me) was rapidly isomerised to the ester (X; R = Me), m. p. 174°, previously obtained [7] by lactonisation of the dibasic acid (XII; R = R′ = H) followed by methylation. That the isomerisation occurred without opening of the lactone ring was shown by solvent-extraction of the ester (X; R = Me) from the alkaline reaction medium. However, some opening of the lactone ring and hydrolysis of the ester group took place during the reaction, and the acids (X; R = H) and (XII; R = Me or H, R′ = H), isolated as their esters, were present in the acidic fraction of the products. The ester (X; R = Me) was occasionally obtained as the hydrate which readily afforded the anhydrous ester on drying *in vacuo*. Progressively more vigorous alkaline hydrolysis of the ester (X; R = Me) gave, sequentially, the half-ester (XII; R = Me, R′ = H) and the dibasic acid (XII; R = R′ = H), both isolated, after methylation, as the diester [7] (XII; R = R′ = Me).

The axial configuration of the 2-hydroxyl substituent in the ester (X; R = Me) follows from the isolation of the same acid (XV), known [11] to be in the 8-epimethyl series, after hydrogenolysis with Adams catalyst in glacial acetic acid of both methyl gibberellate and the ester (X; R = Me). In 1,3-disubstituted gibbanes an axial 2-hydroxy-substituent is in the more stable configuration.

The acid (XII; R = R′ = H) was obtained by the action of 0·1N-sodium hydroxide on gibberellic acid; [7] but with more dilute alkali, or less rapidly, in aqueous solution at room temperature, gibberellic acid undergoes rearrangement to the amorphous acid



Reagents: 1, OH^-. 2, O_3. 3, Heat 110°. 4, CH_2N_2. 5, H_2–Pt. 6, H^+, 100°. 7, $NaIO_4$. 8, HCl–MeOH.

(X; R = H), isolated as the hydrate and identified by methylation to the ester (X; R = Me).

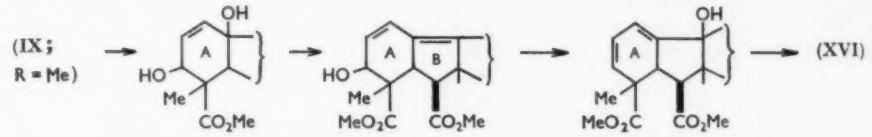
The ratio of the R_F's of the acid (X; R = H) and gibberellic acid is 0·82 : 1·00 in

[11] Grove and McCloskey, unpublished work.

butanol–ammonia;[12] and the acid (X; R = H) is responsible for the spot at R_F 0·35 detected[12] in aged aqueous solutions of gibberellic acid and sometimes when pure gibberellic acid is run in butanol–ammonia at elevated temperatures. The most convenient method of preparation of the acid (X; R = H) from gibberellic acid is to allow the isomerisation to take place at room temperature in aqueous 0·1N-ammonia.

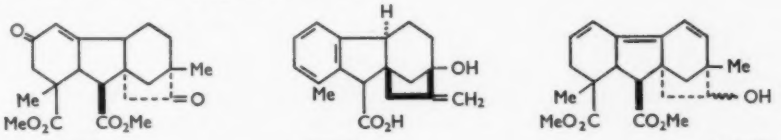
In aqueous solution at room temperature conversion of gibberellic acid into the acid (X; R = H) and into gibberellenic acid (VIII) occurs simultaneously (by mechanisms which are probably mutually exclusive), production of the former being favoured by high pH and of the latter by low pH.

Treatment of methyl gibberellate with methanolic hydrogen chloride gave, in addition to methyl gibberate (XIII; R = Me; 4bα) and epigibberate (XIII; R = Me; 4bβ), a conjugated triene $C_{21}H_{24}O_5$ (XVI) formed by way of (XVIII)—(XX). In this



(XVIII) (XIX) (XX)

reaction sequence methanolysis of the 1 ⟶ 4a-lactone bridge and dehydration of the alcohol (XVIII) are followed by allylic rearrangement of the dienol (XIX) to the alcohol (XX) and then by a second dehydration and migration of the conjugated system of double bonds to afford the triene (XVI). Under the same conditions the ester (X; R = Me) also gave methyl gibberate, methyl epigibberate, and the triene (XVI). The initial product in the formation of the triene (XVI) from the ester (X; R = Me) is presumably the ester (XII; R = R′ = Me) which undergoes allylic rearrangement to the alcohol (XVIII), and in support of this mechanism the triene (XVI) was obtained both from the ester (XII; R = R′ = Me) and from methyl gibberellenate with boiling dilute mineral acid. In addition to the triene (XVI) much intractable ketonic material of $\lambda_{max.}$ 242 mμ was formed in all these reactions. The material of $\lambda_{max.}$ 242 mμ is unlikely to be the ketone (XXI), arising from dehydration of the α-glycol system in (XII; R = R′ = Me) since it is also formed from methyl gibberellenate.



(XXI) (XXII) (XXIII)

Although the gibb-4-enes (X, R = H or Me; and XII; R = R′ = H) gave carbon dioxide and gibberic acid (or its methyl ester) with boiling dilute mineral acid, they were stable to acid at room temperature and were recovered under conditions where gibberellic acid gave gibberellenic[10] or allogibberic acid (XXII).[12] Like gibberellic acid[1] the acid (X; R = H) gave allogibberic acid with boiling water.

The structure of the triene (XVI) was deduced as follows. It contained two methoxyl and a ketone group (oxime). The infrared spectrum showed no bands due to OH absorption and only one C=O band (at 1736 cm.$^{-1}$) which was assigned to two ester groups and a five-membered ring ketone. This ketone group was not conjugated with the main chromophoric system which persisted without modification in the alcohol $C_{21}H_{26}O_5$ (XXIII) obtained by reduction of the triene ketone (XVI) with sodium borohydride. Any gross rearrangement of the carbon skeleton is unlikely to be involved in the formation of

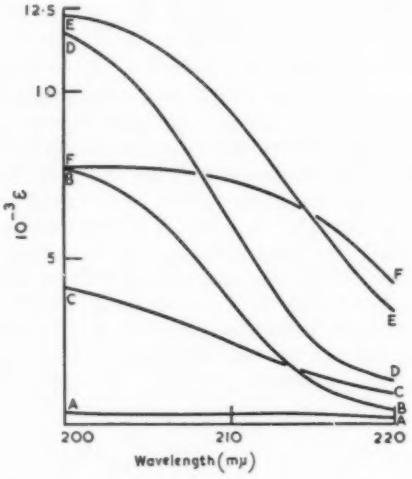
[12] Brian, Grove, Hemming, Mulholland, and Radley, *Plant Physiol.*, 1958, **33**, 329.

the triene since dehydrogenation by selenium gave 1,7-dimethylfluorene. By analogy with other ketonic C/D rearrangement products [6] the compound is assigned the 7α-gibbane stereochemistry: the optical rotatory dispersion revealed a very strong positive plain curve down to 320 mμ and the sign of the Cotton effect could not be determined.

In presence of a palladium catalyst the triene gave a tetrahydro-compound, $C_{21}H_{28}O_5$ (XXIV), which contained a tetrasubstituted ethylenic double bond exocyclic to two rings ($\lambda_{max.}$ 204 mμ, log ε 4·06).[13] The principal ultraviolet maximum, at 287 mμ, of the triene is in fair agreement with that expected for the 3,4a(4b),5-triene (XVI), both by calculation,[14] which gives 274 mμ, and by 30 mμ extension of the chromophore of gibberellenic acid (VIII) ($\lambda_{max.}$ 253 mμ); it is inconsistent with that calculated (313 mμ) for the alternative 2,4,4b-triene which contains a homoannular diene system.

The formation of the triene (XVI) provides conclusive evidence for the position of the lactone bridge in gibberellic acid (cf. ref. 7).

The increase in absorption intensity (ε 9300) at 210 mμ in the ester (X; R = Me) (see Figure) compared with that (ε 6200) of methyl gibberellate is consistent with the



Ultraviolet absorption of (A) *methyl tetrahydrogibberellate,* (B) *gibberellin* A_1 *methyl ester,* (D) *methyl gibberellate, and the esters* (E) (X; R = Me) *and* (F) (XXV; m. p. 232—235°). (C) *is the subtraction curve* (D − B).

change from a disubstituted to a trisubstituted double bond in the former compound; and evidence for this substitution pattern also comes from the infrared spectrum ($\nu_{max.}$ 820 cm.$^{-1}$) and from the nuclear magnetic resonance spectrum [15] of the acetyl derivative. But since some features of the nuclear magnetic resonance spectrum were difficult to reconcile with structure (X; R = Me) the chemistry of the ester was investigated more fully. In agreement with structure (X; R = Me) the ester was not oxidised by manganese dioxide in chloroform,[7] and hydrogenation over a palladium catalyst gave mainly acidic products resulting from hydrogenolysis of the lactone ring. The trisubstituted double bond was difficult to reduce and after uptake of 1 mol. of hydrogen the neutral portion of the product consisted essentially of a mixture of dihydro-compounds (XXV), m. p. 171—172° and m. p. 232—235°, epimeric at position 8. These compounds are known [11] to belong to the 8-methyl and 8-epimethyl series respectively.

Ozonolysis of the ester (X; R = Me) took the same course as the ozonolysis of methyl

[13] Ellington and Meakins, *J.*, 1960, 697.
[14] Fieser and Fieser, "Natural Products related to Phenanthrene," 3rd edn., Reinhold, New York, 1949, p. 187.
[15] Sheppard, *J.*, 1960, 3040.

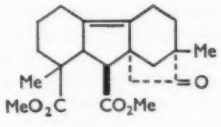
gibberellate,[7] giving formaldehyde, an α-ketol $C_{19}H_{22}O_7$ (XI; R = R′ = H), and a keto-acid $C_{19}H_{22}O_8$ (XIV; R = H) as main products. Periodate oxidation of the ketol (XI; R = R′ = H) afforded the keto-acid (XIV; R = H).

Aromatisation of the keto-acid (XIV; R = H) or its methyl ester with boiling dilute mineral acid gave (after methylation as appropriate) the keto-ester (XVII), previously obtained [1] by degradation of allogibberic acid and of known stereochemistry. It follows from this, and from the fact that the optical rotatory dispersion curve of the ketol (XI; R = R′ = H) showed a positive Cotton effect (cf. ref. 6), that the structure and stereochemistry of rings B/C/D in the ester (X; R = Me) are the same as in methyl gibberellate.

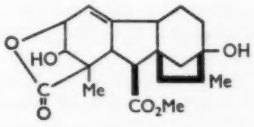
A number of by-products were isolated after the ozonolysis of the ester (X; R = Me). When the reaction was carried out in ethyl acetate at −70° a substance $C_{19}H_{22}O_7$, m. p. 206—208°, an α-ketol $C_{19}H_{22}O_8$, and the corresponding keto-acid $C_{19}H_{22}O_9$ (also obtained by periodate oxidation of the ketol and isolated as the methyl ester, m. p. 202—204°) were formed in low yield. The acetyl derivative $C_{22}H_{26}O_{10}$ of the ester, m. p. 202—204°, showed no hydroxyl absorption in the infrared spectrum, and the additional oxygen atom in the ketol $C_{19}H_{22}O_8$ and in its degradation products is considered to be in an epoxide ring (see XXVI). The absence of an ethylenic double bond in this series of compounds was confirmed by the weak ultraviolet end-absorption of the ester, m. p. 202—204°, which took up no hydrogen on attempted catalytic reduction and failed to aromatise when boiled with dilute mineral acid. Finally, oxidation of the ketol (XI; R = R′ = H) with perbenzoic acid gave the ketol $C_{19}H_{22}O_8$.

None of the above by-products was obtained when the ozonolysis was carried out in acetic acid at 20°; instead, a substance, $C_{21}H_{24}O_8$, m. p. 173—174°, was obtained in low yield; it was shown to be the 7-acetate (XI; R = H, R′ = Ac) of the ketol since it was not affected by periodate and acetylation gave the diacetate (XI; R = R′ = Ac).

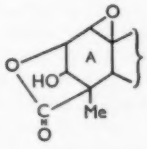
The ultraviolet end-absorption of gibberellin A_1 methyl ester (see Figure, curve B) was consistent with the presence of a $>C{=}CH_2$ group in this compound, and the subtraction curve (C) [= (D) − (B)] was consistent with a 1,2-disubstituted *cis*-ethylenic bond in methyl gibberellate (curve D). The trisubstituted double bond in ring A of the esters (X; R = Me) (curve E) and (XXV) (m. p. 232—235°; curve F) gave a very broad absorption band similar to that reported [13] for some Δ^7-steroids.



(XXIV)



(XXV)



(XXVI)

The decomposition product gibberellenic acid is present in small amounts in gibberellic acid when this is obtained by solvent-extraction of *Gibberella fujikuroi* broths [16] followed by crystallisation from ethyl acetate–light petroleum. It is readily detected and estimated by the characteristic ultraviolet absorption at 253 mμ, but not by the infrared spectrum which (in Nujol) has few strong bands, most of which are present in the spectrum of gibberellic acid. It can be removed from the crude gibberellic acid by chromatography on "Celite" buffered at pH 7, gibberellenic acid being retained on the column, or by crystallisation from aqueous methanol. The latter method sometimes gives gibberellic acid as a hydrate which can be recognised by its characteristic infrared spectrum and readily yields the anhydrous acid *in vacuo*.

[16] Gerzon, Bird, and Woolf, *Experientia*, 1957, **13**, 487.

XUM

Methyl gibberellate tenaciously retained solvent of crystallisation, and neither chloroform nor ether was removed at 100° *in vacuo*. Benzene was removed at 130° from preparations crystallised [17] from benzene–methanol, and the infrared spectrum of the solvent-free material was identical with that of methyl gibberellate crystallised from aqueous methanol or aqueous ethanol. Crystallisation from ethyl acetate gave a different solvent-free crystalline modification, characterised by its infrared spectrum.

With an excess of ethereal diazomethane in methanol methyl gibberellate gave, in low yield, a substance $C_{21}H_{26}O_6N_2$ which no longer gave the characteristic red colour with concentrated sulphuric acid [17] but gave a positive Knorr test. From the infrared ($\nu_{max.}$ 1552 cm.$^{-1}$) and ultraviolet ($\lambda_{max.}$ 324 mμ; log ε 2·56) spectra which are consistent with the presence of the N=N grouping, it is presumably the 1-pyrazoline resulting from the addition of diazomethane to the double bond in ring A of methyl gibberellate.

Experimental

M. p.s are corrected. Alumina of grade II and pH 4, and Celite 545, were used in chromatography. Unless otherwise stated, infrared spectra were obtained for Nujol mulls, and ultraviolet spectra and optical rotations for ethanol solutions. Optical rotatory dispersion curves were obtained for methanol solutions. Ultraviolet end-absorption data were obtained with a Unicam S.P. 500 spectrophotometer as described by Bladon *et al.*[18] Light petroleum had b. p. 60—80°. Microhydrogenations were carried out in acetic acid with a palladium-black catalyst.

Gibberellic Acid Hydrate.—Gibberellic acid (50 mg.) was dissolved in ethanol (25 ml.) and water (10 ml.). After removal of the ethanol and concentration *in vacuo*, the aqueous solution was set aside at 0° for 48 hr. The *hydrate* crystallised in prisms (25 mg.), m. p. (tube) 236° (decomp.) after softening at 190°, (Kofler block; rapid heating) 185—210° (Found: C, 63·0; H, 6·6. $C_{19}H_{22}O_6,H_2O$ requires C, 62·6; H, 6·6%), $\nu_{max.}$ 3413, 3240 (broad) (OH); 2660, 2584 (carboxylic OH); 1766, 1716 (C=O); ~1686 (H_2O?); 1653 (C=C). Between 7 and 15 μ the infrared spectrum differed considerably from that of anhydrous gibberellic acid. Anhydrous gibberellic acid (Found: C, 65·7; H, 6·6. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·4%) was obtained on drying the hydrate *in vacuo* at 100° for 6 hr. over phosphorus pentoxide. With concentrated sulphuric acid the hydrate gave the same red colour and blue fluorescence as were given by gibberellic acid.

Purification of Gibberellic Acid.—(a) *By chromatography.* Crude gibberellic acid [100 mg.; m. p. 218—220° (decomp.), $E^{1\%}_{1\,cm.}$ 14 at 253 mμ], containing gibberellenic acid [10] (2·1%), in ether (300 ml.) was chromatographed on Celite (15 g.; 24 × 1·5 cm.) buffered at pH 7·0 (Sørensen M/15-phosphate buffer; 10 ml.). Elution (250 ml. fractions) was effected with ether previously saturated with water. Fractions 1—3 (10 mg.) contained intractable amorphous material. Fractions 4—15 (74 mg.) crystallised from ethyl acetate–light petroleum, giving gibberellic acid (66 mg.), m. p. 232—234° (decomp.), $[\alpha]_D^{26}$ +93° (*c* 0·4), $E^{1\%}_{1\,cm.}$ 5·0 at 253 mμ, free from gibberellenic acid (Found: C, 65·5; H, 6·5. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·4%). Fractions 16—17 (15 mg.) furnished a powder, m. p. 215° (decomp.), $[\alpha]_D^{20}$ +75° (*c* 0·75), $\lambda_{max.}$ 255 mμ ($E^{1\%}_{1\,cm.}$ 16), consisting mainly of gibberellic acid (gibberellenic acid content, 2·3%). The infrared spectrum was indistinguishable from that of pure gibberellic acid.

*Gibberellic acid toluene-*p*-sulphonate*, prepared in pyridine during 3 days at room temperature, was obtained as an amorphous powder, m. p. 150° (decomp.), by addition of light petroleum to an ethyl acetate solution of the crude product. Recrystallisation from boiling toluene (losses) gave prisms, m. p. 152—155° (decomp.) (Found: C, 62·4; H, 5·95. $C_{26}H_{28}O_8S$ requires C, 62·4; H, 5·6%).

(b) *By crystallisation.* Water (65 ml.) was added to the crude gibberellic acid (5·0 g.) in methanol (24 ml.), and the solution was set aside for 18 hr. at 0°. Prisms (4·0 g.) of gibberellic acid, m. p. 232—233° (decomp.), $[\alpha]_D^{20}$ +89° (*c* 1·07), $E^{1\%}_{1\,cm.}$ 5·8 at 253 mμ, were obtained. The product resulting from this method of purification was frequently gibberellic acid hydrate.

Methyl Gibberellate (IX; R = Me).—Methyl gibberellate [17] crystallised from ethyl acetate in needles, m. p. 205—207° (Found, in sample dried at 20° *in vacuo*: C, 66·7; H, 6·8. Calc. for

[17] Cross, *J.*, 1954, 4670.
[18] Bladon, Henbest, and Wood, *J.*, 1952, 2737.

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$C_{20}H_{24}O_6$: C, 66·65; H, 6·7%), $\nu_{max.}$ 3510, 3320 (OH); 1768, 1737 cm.$^{-1}$ (C=O). The infrared spectrum differed, particularly in the 7—15 μ region, from that of methyl gibberellate crystallised from benzene–methanol and dried [17] at 130° [$\nu_{max.}$ 3575, 3500 (OH); 1765, 1735w, 1710 cm.$^{-1}$ (C=O)]. The spectra of methyl gibberellate crystallised from ethyl acetate–light petroleum or from benzene–methanol but dried at 20° were identical except that the latter preparation gave a strong broad absorption at 690 cm.$^{-1}$ absent from the former. From 7 to 14 μ the spectra were essentially the same as that found for methyl gibberellate crystallised from ethyl acetate, but the C=O region showed strong bands at 1770, 1730, and 1712 cm.$^{-1}$.

Methyl gibberellate crystallised from aqueous ethanol in plates, m. p. 182—192°, $[\alpha]_D^{22}$ +80° (*c* 2·0) (Found: C, 66·9; H, 6·8%). The infrared spectrum was unaffected when the ester was dried at 100° *in vacuo* and was identical with that of methyl gibberellate crystallised from benzene–methanol and dried at 130°. Plates, m. p. 192—197°, with the same infrared spectrum were obtained from aqueous methanol.

Methyl gibberellate crystallised from ether in needles of the *ether solva e*, m. p. 170—172° (Found, in sample dried at 100° *in vacuo*: C, 66·1; H, 7·6. $C_{20}H_{24}O_6$,$C_4H_{10}O$ requires C, 66·3; H, 7·9%), $\nu_{max.}$ 3490sh, 3320, 3260 (OH): 1773, 1737 cm.$^{-1}$ (C=O). Needles of a *solvate*, m. p. 192—195°, were obtained from chloroform (Found, in sample dried at 100° *in vacuo*: C, 52·4; H, 5·3; Cl, 20·1. $C_{20}H_{24}O_6$,$CHCl_3$ requires C, 52·6; H, 5·25; Cl, 22·2%), $\nu_{max.}$ 3330 (OH); 1768, 1738 cm.$^{-1}$ (C=O).

Reaction of Diazomethane with Methyl Gibberellate.—Gibberellic acid (173 mg.) in methanol (2 ml.) was treated with diazomethane (105 mg., 5 mol.) in ether (10 ml.) during 48 hr. After removal of the solvents and excess of diazomethane *in vacuo*, the product, in benzene–methanol (200 : 1), was chromatographed on alumina (15 × 1·5 cm.). Elution with benzene–methanol (200 : 1; 350 ml.) and crystallisation from ethyl acetate–light petroleum afforded methyl gibberellate (117 mg.), m. p. 200—203°. Further elution of the column with benzene–methanol (50 : 1; 200 ml.) gave a gum (9 mg.) which crystallised from ethyl acetate–light petroleum in prisms, m. p. 232—234°, $[\alpha]_D^{17}$ +135° (*c* 0·4), of a *pyrazoline* (Found: C, 62·6; H, 6·6; N, 7·2. $C_{21}H_{26}O_6N_2$ requires C, 62·7; H, 6·5; N, 7·0%), $\lambda_{max.}$ 324 mμ (log ε 2·56), $\nu_{max.}$ 3515 (OH); 1772, 1719 (C=O); 1552 (N=H); 3080, 901 cm.$^{-1}$ (C=CH_2). It was less soluble than methyl gibberellate in ethyl acetate and gave a colourless solution in concentrated sulphuric acid. It gave a dark red colour with concentrated sulphuric acid and potassium dichromate.

Action of Alkali on Gibberellin A_1 Methyl Ester [*Methyl 1-Carboxy-2(ax),4a,7-trihydroxy-1-methyl-8-methylenegibbane-10-carboxylate* 1 ⟶ 4a-*Lactone*] (II; R = Me).—(*a*) The finely powdered ester (100 mg.) was shaken with 0·01N-sodium hydroxide (45·0 ml.) at room temperature until it dissolved (2·5 hr.). Back-titration with 0·1N-hydrochloric acid showed that 0·18 equiv. of alkali had been consumed. The aqueous solution (pH 7) was extracted with ether giving, on recovery, a neutral fraction (44 mg.). The aqueous layer was acidified to pH 2 with concentrated hydrochloric acid and re-extracted with ether. The extract was separated into neutral (17 mg.) and acidic (7 mg.) fractions by extraction with sodium hydrogen carbonate and recovery.

The acid fraction crystallised from ethyl acetate–light petroleum in prisms (2 mg.), m. p. 236—240° (decomp.), of gibberellin A_1 identified by the infrared spectrum.

The combined neutral fractions (61 mg.), in benzene–methanol (200 : 1; 100 ml.), were chromatographed on alumina (15 × 1·5 cm.) and eluted as follows: (i) benzene–methanol (200 : 1; 200 ml.) gave gibberellin A_1 methyl ester (34 mg.), m. p. 232—234°, (ii) benzene–methanol (200 : 1; 200 ml.) gave intractable mixtures (3 mg.), and (iii) benzene–methanol (50 : 1; 100 ml.) gave the 2(eq)-*hydroxy-epimer* (23 mg.), prisms, m. p. 193°, $[\alpha]_D^{15}$ +42° (*c* 0·5) (from ethyl acetate–light petroleum) (Found: C, 66·3; H, 7·3. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%), $\nu_{max.}$ 3470, 3430 (OH); 1773, 1707 (C=O); 1657 cm.$^{-1}$ (C=C).

Takahashi *et al.*[8] give m. p. 182—183° for pseudogibberellin A_1 methyl ester derived from gibberellin A_1 by treatment with alkali followed by methylation.

(*b*) The ester (325 mg.) and 0·01N-sodium hydroxide (100 ml.) were shaken for 6 hr. and the solution was then acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The acid fraction (106 mg., 33%), obtained as in (*a*), was chromatographed in ether (50 ml.) on Celite (20 × 1·5 cm.; pH 7·0), giving gibberellin A_1 (6 mg.) and intractable gums. The neutral fraction (164 mg., 51%) was separated by chromatography on alumina and fractional crystallisation into gibberellin A_1 methyl ester (35 mg., 11%) and the 2(*eq*)-hydroxy-epimer (80 mg., 25%).

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(*c*) The ester (70 mg.) and 0·01N-sodium hydroxide (45 ml.) were shaken for 2 days and the solution was worked up as in (*b*). No neutral material was obtained. Chromatography of the acid fraction (40 mg.) afforded gibberellin A_1 (2 mg.) and intractable gums (27 mg.).

Action of Alkali on the 2(eq)-*Hydroxy-ester* (II; R = Me).—The ester (31 mg.) was shaken with 0·01N-sodium hydroxide (15 ml.) for 2 hr. Dissolution was complete in 10 min. Extraction of the acidified solution as described above gave neutral (28 mg.) and acid (3 mg.) fractions. Chromatography of the neutral fraction on alumina (7 × 1 cm.) and fractional elution with benzene–methanol (200 : 1) gave gibberellin A_1 methyl ester (3 mg., 10%), m. p. 231—234°, followed (complete separation of bands) by the 2(*eq*)-hydroxy-epimer (22 mg., 77%), m. p. 189—191°.

The recovered 2(*eq*)-hydroxy-ester was shaken again with 0·01N-sodium hydroxide (10 ml.) as described above, giving gibberellin A_1 methyl ester (2·0 mg.) and starting material (10 mg.).

Action of Alkali on 2(ax),4a-*Dihydroxy*-1,7-*dimethyl*-8-*oxo*-7α-*gibbane*-1,10-*dicarboxylic Acid* 1 ⟶ 4a-*Lactone*[7] (III; R = H).—The lactone (109 mg.) in 0·1N-sodium hydroxide (10 ml.) was set aside for 18 hr. at room temperature and the solution was then acidified with concentrated hydrochloric acid and extracted with ethyl acetate. Fractional crystallisation of the product from ethyl acetate gave materials, (i) m. p. 258—262° (decomp.) (47 mg.), (ii) m. p. 257—260° (decomp.) (16 mg.), (iii) m. p. 225—235° (decomp.) (14 mg.), and (iv) gums (10 mg.).

Fractions (i) and (ii) were combined and recrystallised from ethyl acetate, giving the 2(eq)-*hydroxy-lactone* (51 mg.), m. p. 262—264° (decomp.), $[\alpha]_D^{21}$ +48° (*c* 1·0) (Found: C, 65·3; H, 7·0. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·9%), $\nu_{max.}$ 3425 (OH); 1778, 1726 (broad) cm.$^{-1}$ (C=O). A mixed m. p. determination with the 2(*ax*)-hydroxy-epimer (III; R = H) showed a 25° depression. Takahashi *et al.*[9] give m. p. 260—262° for isogibberellin A_1 obtained by treatment of gibberellin C with alkali.

The *methyl ester*, prepared with diazomethane, crystallised from ethyl acetate–light petroleum in needles, m. p. 238°, $[\alpha]_D^{18}$ +42° (*c* 0·5 in acetone) (Found: C, 66·6; H, 7·4. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%), $\nu_{max.}$ 3530 (OH); 1762, 1736 (C=O).

Acid Rearrangement of the 2(eq)-*Hydroxy-ester* (II; R = Me).—The ester (17 mg.) in methanol (0·3 ml.) and 3N-hydrochloric acid (3 ml.) was heated under reflux for 1 hr. After removal of the methanol by distillation *in vacuo* the cooled solution was extracted with ethyl acetate. The extract was separated into neutral and acidic fractions by extraction with sodium hydrogen carbonate and recovery. The acid fraction (10 mg.) crystallised from ethyl acetate in prisms, m. p. 257—260° (decomp.), identified (mixed m. p. and the infrared spectrum) as the 2(*eq*)-hydroxy-acid (III; R = H). The neutral fraction (4 mg.) formed needles, m. p. 237—238° (from ethyl acetate–light petroleum), identified as the 2(*eq*)-hydroxy-ester (III; R = Me).

Methyl 1-(*Carboxy*-2(ax),4a,8ξ-*trihydroxy*-1,7-*dimethyl*-7α-*gibbane*-10-*carboxylate* 1 ⟶ 4a-*lactone* (VII).—To a stirred solution of the 2(*ax*)-hydroxy-ester (III; R = Me) (100 mg.) in methanol (10 ml.) at 0° was added sodium borohydride (30 mg.) in methanol (5 ml.). After 1 hr. at room temperature, the excess of borohydride was decomposed by the addition of acetic acid, and the solvent was removed *in vacuo*. After the addition of water (10 ml.), the product was recovered in ethyl acetate and crystallised from ethyl acetate–light petroleum, giving *methyl* 1-*carboxy*-2(ax),4a,8ξ-*trihydroxy*-1,7-*dimethyl*-7α-*gibbane*-10-*carboxylate* 1 ⟶ 4a-*lactone* (VII), needles (50 mg.), m. p. 171—172°, $[\alpha]_D^{16}$ +62° (*c* 1·0) (Found: C, 65·9; H, 7·7. $C_{20}H_{28}O_6$ requires C, 65·9; H, 7·7%), $\nu_{max.}$ 3495, 3370 (OH); 1761, 1730 cm.$^{-1}$ (C=O). Chromatography on alumina of the residue (44 mg.) from the mother-liquors and elution of the column with benzene–methanol (200 : 1) furnished more of the ester (VII), m. p. 170—172° (28 mg.).

Oxidations by Chromic Oxide.—(1) *The ester* (VII). The ester (27 mg.) in acetone (2 ml.) was treated dropwise at 0° with a solution of chromic oxide in sulphuric acid [chromic oxide (66·8 g.) in concentrated sulphuric acid (57·5 ml.) and water (100 ml.), made up to 267 ml.[10]] (0·04 ml.). After 1 hr. at room temperature, water was added and the precipitate was collected and crystallised from ethyl acetate–light petroleum, giving methyl 1-carboxy-4a-hydroxy-1,7-dimethyl-2,8-dioxo-7α-gibbane-10-carboxylate 1 ⟶ 4a-lactone[7] (IV), needles (13 mg.), m. p. 216—218°, identified by mixed m. p. and comparison of the infrared spectra. The products of the following oxidations, carried out in the same way, were identified similarly.

[10] Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457.

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(2) *The* 2(ax)-*hydroxy-ester* (III; R = Me).[7] The ester (20 mg.) gave the diketo-ester (IV) (11 mg.), m. p. 215°.

(3) *The* 2(eq)-*hydroxy-ester* (III; R = Me). The ester (12 mg.) gave the diketo-ester (IV) (9 mg.), m. p. 216°.

(4) *Methyl* 1-*carboxy*-2(eq),4a,7-*trihydroxy*-1,8-*dimethylgibbane*-10-*carboxylate* 1 ⟶ 4a-*lactone* (V; R = Me). The ester (39 mg.) gave prisms (21 mg.), m. p. 160—162°, of methyl 1-carboxy-4a,7-dihydroxy-1,8-dimethyl-2-oxogibbane-10-carboxylate 1 ⟶ 4a-lactone[7] (VI).

(5) *Methyl* 1-*carboxy*-1(eq),4a,7-*trihydroxy*-1,8-*epi-dimethylgibbane*-10-*carboxylate* 1 ⟶ 4a-*lactone* (V; R = Me). The ester (9 mg.) gave needles (7 mg.), m. p. 131—133°, of methyl 1-carboxy-4a,7-dihydroxy-1,8-epi-dimethyl-2-oxogibbane-10-carboxylate 1 ⟶ 4a-lactone[7] (VI).

Alkaline Hydrolysis of the 2(eq)-*Hydroxy-ester* (II; R = Me).—(*a*) The ester (33 mg.) was heated under reflux with N-sodium hydroxide (3 ml.) for 1 hr. and the cooled solution was acidified with concentrated hydrochloric acid. The product, recovered in ethyl acetate, formed prisms (7 mg.), m. p. 227—230° (decomp.), $[\alpha]_D^{19}$ +43° (*c* 0·4) of 2(eq),4a,7-*trihydroxy*-1-*methyl*-8-*methylenegibbane*-1,10-*dicarboxylic acid* 1 ⟶ 4a-*lactone* (II; R = H) (Found: C, 65·3; H, 7·3. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·9%), $\nu_{max.}$ 3415, 3175 (broad) (OH); 1760, 1731 (C=O); 1653 cm.$^{-1}$ (C=C).

The 2(*eq*)-hydroxy-ester (II; R = Me), m. p. 188—191°, was regenerated on methylation of the acid with diazomethane.

(*b*) The ester (45 mg.) was treated as described in (*a*) but the product was crystallised from ethyl acetate–light petroleum, furnishing prisms (30 mg.) which lost solvent on drying at 100° *in vacuo*, giving the *hydrate* of the 2(*eq*)-hydroxy-acid (II; R = H) as an amorphous powder, m. p. 138—145°, resetting and remelting at 205—215° (Found: C, 62·7; H, 7·3%; equiv., 387. $C_{19}H_{24}O_6,H_2O$ requires C, 62·3; H, 7·15%; *M*, 366), $\nu_{max.}$ 3395 (broad) (OH); 1763, 1720 (C=O), 1650 (broad) cm.$^{-1}$ (H_2O, C=C). The anhydrous acid, m. p. 227—230° (decomp.), was obtained by drying the hydrate at 130—140° *in vacuo* and crystallising the gummy product from ethyl acetate.

Takahashi *et al.*[8] give m. p. 225—227° (decomp.), $[\alpha]_D^{23}$ +34° (*c* 3·9), for pseudogibberellin A_1 obtained by the action of alkali on gibberellin A_1.

Action of Alkali on Methyl Tetrahydrogibberellate (V; R = Me).—The finely powdered ester (220 mg.) was shaken with 0·01N-sodium hydroxide (150 ml.) at 24—26° for 6 hr. by which time dissolution was almost complete. The mixture was extracted with ethyl acetate, and the organic layer was washed with sodium hydrogen carbonate and evaporated, giving a solid (208 mg.). Acidification of the aqueous layer and washings followed by extraction with ethyl acetate yielded an intractable acidic gum (14 mg.). The neutral solid in methanol (3 ml.) and benzene (150 ml.) was chromatographed on alumina (13 × 1·7 cm.) and the column was eluted with 100 ml. portions of benzene–methanol (ratios in parentheses), giving the following fractions: (i)—(ii) (200 : 1) intractable gum (25 mg.), (iii)—(vi) (200 : 1) solid (78 mg., 35%), m. p. 246—266° [recrystallisation from aqueous methanol gave methyl tetrahydrogibberellate, m. p. 262—268° (75 mg., 34%)], (vii)—(ix) (100 : 1) interband (12 mg.), (x)—(xii) (50 : 1) solid (78 mg., 38%), m. p. 203—209°. Recrystallisation of the last material from aqueous methanol or ethyl acetate–light petroleum gave the 2(eq)-*hydroxy-epimer* of methyl tetrahydrogibberellate as rods or prisms (63 mg., 29%), m. p. 212—214° and 235—239°, $[\alpha]_D^{20}$ +59° (*c* 1·0) (Found: C, 65·6; H, 7·8. $C_{20}H_{28}O_6$ requires C, 65·9; H, 7·7%), $\nu_{max.}$ 3460 (OH); 1782, 1764, 1712 cm.$^{-1}$ (C=O); in $CHCl_3$, 1767 and 1732 cm.$^{-1}$.

Action of Alkali on the Mixed Methyl Tetrahydrogibberellates (8-*Epimers*).—The finely powdered mixture of esters (360 mg.) obtained by hydrogenation of methyl gibberellate[7] was shaken with 0·01N-sodium hydroxide (225 ml.) for 7·5 hr. The solid dissolved almost at once. After acidification the solution was extracted with ethyl acetate, and the organic layer was washed with sodium hydrogen carbonate. Acidification of the washings and recovery gave an intractable acidic gum (38 mg.). The neutral fraction (299 mg.) in methanol (4 ml.) and benzene (200 ml.) was chromatographed on alumina (16 × 2·2 cm.), and the column was eluted as follows: Fractions (i), benzene–methanol (200 : 1; 1800 ml.), and (ii) benzene–methanol (100 : 1, 600 ml.), gave mixtures (70 mg.) of methyl tetrahydrogibberellates, epimeric at $C_{(8)}$. Fraction (iii), benzene–methanol (50 : 1; 200 ml.), crystallised from ethyl acetate–light petroleum in prisms (15 mg.), m. p. 166—168°, of *methyl* 1-*carboxy*-2(eq),4a,7-*trihydroxy*-1,8-*epi-dimethylgibbane*-10-*carboxylate* 1 ⟶ 4a-*lactone* (V; R = Me) (Found: C, 66·0; H, 7·7. $C_{20}H_{28}O_6$

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requires C, 65·9; H, 7·7%), $[\alpha]_D^{18}$ +46° (*c* 0·7), $[\alpha]_D^{18}$ +43° (*c* 0·5 in acetone), $\nu_{max.}$ 3475, 3270 (shoulder) (OH); 1785, 1775 (shoulder), 1711 cm.$^{-1}$ (C=O); in $CHCl_3$, 1771, 1734 cm.$^{-1}$. The ester was sometimes obtained in solvated prisms, m. p. 95° (gas evolution) and 166—168°. Solvent-free material, m. p. 166—168°, was obtained by drying *in vacuo* at 65° and the m. p. was raised on admixture with the 8-epimer of m. p. 212—214° (235—239°). Fractions (iv) and (v), benzene–methanol (50 : 1; 200 ml.), furnished prisms (79 mg.), m. p. 165—178°, and (55 mg.), m. p. 193—199°, respectively, which are presumed to be mixtures of the 8-epimeric 2(*eq*)-hydroxy-compounds (V; R = Me). Fraction (vi), benzene–methanol (50 : 1; 200 ml.), crystallised from ethyl acetate–light petroleum in blades (28 mg.), m. p. 209—214°. Recrystallisation from aqueous methanol gave prisms, m. p. 212—214° and 235—239° of the above 2(*eq*)-hydroxy-8-methyl compound (V; R = Me).

Hydrogenation of the 2(eq)-*Hydroxy-ester* (II; R = Me).—(*a*) The ester (36 mg.) in ethyl acetate (5 ml.) was reduced with hydrogen (2·4 ml., 1·08 mol.) at room temperature in the presence of 10% palladium–charcoal (36 mg.). The gummy product (36 mg.) crystallised from ethyl acetate–light petroleum in needles (15 mg.), m. p. 181—184°, comprising a mixture of dihydro-compounds (V; R = Me) epimeric at position 8, which could not be separated by fractional crystallisation (Found: C, 65·8; H, 7·8. Calc. for $C_{20}H_{28}O_6$: C, 65·9; H, 7·7%), $\nu_{max.}$ 3470 (OH); 1782, 1772 (sh), 1711 cm.$^{-1}$ (C=O).

(*b*) The ester (180 mg.) in ethyl acetate (40 ml.) in the presence of 10% palladium–charcoal (180 mg.) was hydrogenated as in (*a*) (uptake 1·1 mol.). The gummy product (177 mg.) in benzene (100 ml.) was chromatographed on alumina (15 × 1 cm.), and the column was eluted as follows: Fraction (i) [benzene–methanol (200 : 1; 500 ml.)] was a gum (110 mg.), which crystallised from ethyl acetate–light petroleum in prisms (40 mg.) of the 2(*eq*)-hydroxy-8-epimethyl ester (V; R = Me), m. p. 165—166°. Fractions (ii) [benzene–methanol (200 : 1, 300 ml.)], and (iii) [benzene–methanol (100 : 1; 100 ml.)] furnished mixtures (10 and 20 mg. respectively). Fraction (iv) [benzene–methanol (100 : 1; 300 ml.)], a gum (38 mg.), crystallised from ethyl acetate–light petroleum in prisms (33 mg.) of the 8-methyl epimer (V; R = Me), double m. p. 212—214° and 235—239°.

Hydrogenation of the 2(eq)-*Hydroxy-acid* (II; R = H).—The acid (3·02 mg.) was subjected to microhydrogenation (uptake: 0·15 ml., 0·77 mol.). The product crystallised from ethyl acetate–methanol in prisms, m. p. 280—282° (decomp.), of the dihydro-derivative. The infrared spectrum was identical with that of authentic dihydropseudogibberellin A_1, m. p. 290—291° (decomp.),[8] kindly provided by Professor Sumiki. The decomposition point varied with the particle size and rate of heating.

The dihydro-compound (3 mg.) in methanol with ethereal diazomethane gave prisms (2 mg.), m. p. 176—181° (from ethyl acetate–light petroleum). The infrared spectrum was identical with that of the mixture, m. p. 181—184°, of 8-epimeric dihydro-compounds obtained by hydrogenation of the 2(*eq*)-hydroxy-ester (II; R = Me).

Reduction of the Ketone (VI), *m. p.* 161—163°.—The ketone (100 mg.) in methanol (10 ml.) at 0° was stirred for 1 hr. during the addition of sodium borohydride (30 mg.) in methanol (5 ml.). Excess of hydride was destroyed by the addition of acetic acid, and the solution was concentrated to small bulk *in vacuo*. After the addition of water (10 ml.), the product, an amorphous powder (97 mg.), was recovered in ethyl acetate. A portion (70 mg.) in benzene–methanol (200 : 1; 50 ml.) was chromatographed on alumina (7 × 1 cm.) and the column was eluted as follows (all fractions were gums): (i) benzene–methanol (200 : 1; 200 ml.) gave 11 mg., which crystallised from ethyl acetate in prisms (7 mg., 10%), m. p. 260—263°, of methyl tetragibberellate (V; R = Me); (ii) benzene–methanol (200 : 1; 100 ml.; followed by 100 : 1, 200 ml.) gave 53 mg., which crystallised from ethyl acetate–light petroleum in prisms (36 mg., 51%), m. p. 212—216° and 235—239°, of the 2(*eq*)-hydroxy-epimer (V; R = Me) of methyl tetrahydrogibberellate.

The identities of both products were confirmed by comparison of the infrared spectra.

Action of Sodium Hydroxide on Gibberellenic Acid[10] (VIII).—The acid (28 mg.) in 0·1N-sodium hydroxide (6 ml.) was set aside for 48 hr. The solution was cooled to 0°, acidified to pH 3 by 2N-hydrochloric acid, and immediately extracted with ethyl acetate. Gibberellenic acid (15 mg.), m. p. 178—179° (from ethyl acetate), was recovered from the extracted material (23 mg.).

A similar recovery of gibberellenic acid was obtained (by Dr. J. S. Moffatt) after 5 hr. by using 0·02N-sodium hydroxide.

Action of Alkali on Methyl Gibberellate.—(*a*) Methyl gibberellate (100 mg.) and 0·01N-sodium hydroxide (45 ml.) were shaken at 24°, a clear solution being obtained after 5 min. After 2 hr. back-titration with 0·1N-hydrochloric acid showed that 0·62 equiv. of alkali had been consumed. Extraction of the solution at pH 7 with ether yielded a neutral fraction (27 mg.). The solution was then acidified to pH 2 with concentrated hydrochloric acid and re-extracted with ether. The ethereal layer was extracted with sodium hydrogen carbonate, and neutral (15 mg.) and the intractable gummy acidic (10 mg.) fractions were recovered. The combined neutral fractions in benzene–methanol (200 : 1) were chromatographed on alumina (15 × 1 cm.), and the column was eluted with nine 100-ml. portions of benzene–methanol (200 : 1). All eluates yielded methyl 1-carboxy-2(*ax*),3,7-trihydroxy-1-methyl-8-methylenegibb-4-ene-10-carboxylate 1 ⟶ 3-lactone [7] (X; R = Me), obtained, after recrystallisation from ethyl acetate–light petroleum, as prisms (20 mg.), m. p. 172—173°, and identified by mixed m. p. and comparison of the infrared spectra.

Like methyl gibberellate the ester (X; R = Me) in concentrated sulphuric acid gave a wine-red colour which developed a blue fluorescence. Microhydrogenation resulted in the uptake of 1·87 mol.

The *hydrate* crystallised from ethyl acetate–light petroleum in prisms, m. p. 102—106° (gas evolution) and 172° (Found: C, 62·9; H, 7·1. $C_{20}H_{24}O_6,H_2O$ requires C, 63·5; H, 6·9%), $\nu_{max.}$ 3495, 3410, 3305 (OH); 1765, 1743, 1715 (C=O); 1676 (C=C); 1637 (broad) cm.$^{-1}$ (C=C, H_2O); in acetonitrile, 1773, 1730; ~1672 cm.$^{-1}$. The infrared spectrum in acetonitrile was identical with that of the anhydrous ester in the same solvent. The hydrate lost water *in vacuo* at 80° (2 hr.) and the infrared spectrum of the product was identical with that of the anhydrous ester.

The *acetate*, prepared in pyridine with acetic anhydride during 24 hr. at room temperature, crystallised from ethyl acetate–light petroleum in prisms, m. p. 165—166° (Found: C, 65·85; H, 6·9. $C_{22}H_{26}O_7$ requires C, 65·7; H, 6·5%), $\nu_{max.}$ 3520 (OH); 1773, 1728, 1718 cm.$^{-1}$ (C=O). It was readily soluble in chloroform.[15]

The *benzoate hemihydrate* was prepared by the addition of benzoyl chloride (0·05 ml.) to the ester (100 mg.) in pyridine (0·5 ml.). After 48 hr. at room temperature the solvent was removed *in vacuo*, water was added to the semi-solid residue, and the resulting suspension was extracted with ether. The ether extract was washed with sodium hydrogen carbonate and concentrated to small volume. The solid product obtained by addition of light petroleum (b. p. 40—60°) to this solution was purified by two further precipitations from ether by light petroleum (b. p. 40—60°) and formed an amorphous powder (85 mg.), m. p. 90—95° (gas evolution) (Found: C, 68·1; H, 6·5. $C_{27}H_{28}O_7,0{\cdot}5H_2O$ requires C, 68·5; H, 6·2%), $\nu_{max.}$ 3450 (very broad), (OH); 1780, 1730 (C=O); 1670 (C=C); 1650 (C=C, H_2O); 1600, 715 cm.$^{-1}$ (aromatic ring). The m. p. and infrared spectrum were unaltered on drying *in vacuo* at 63°.

(*b*) Methyl gibberellate (500 mg.) was shaken with 0·01N-sodium hydroxide as described in (*a*) and the product obtained by extraction of the acidified solution with ethyl acetate was separated into neutral (200 mg.) and acidic (160 mg.) fractions. The neutral fraction crystallised from ethyl acetate–light petroleum in prisms (129 mg., 26%), m. p. 174°, of the ester (X; R = Me).

A portion (30 mg.) of the amorphous acid fraction, m. p. 116—132° (decomp.), was treated with diazomethane, and the gummy product in benzene–methanol (200 : 1; 50 ml.) was chromatographed on alumina (15 × 1 cm.). The column was eluted as follows: (i) benzene–methanol (100 : 1; 150 ml.) gave the ester (X; R = Me) as prisms (5 mg.), m. p. 173—174°, from ethyl acetate–light petroleum; (ii) benzene–methanol (50 : 1; 250 ml.) gave methyl 2,3,7-trihydroxy-1-methyl-8-methylenegibb-4-ene-1,10-dicarboxylate [7] (XII; R = R′ = Me), prisms (21 mg.), m. p. 97—105° (gas evolution) (from methanol), identified by comparison of the infrared spectra.

(*c*) Methyl gibberellate (200 mg.) in 0·01N-sodium hydroxide (90 ml.) was shaken for 1 hr. and the alkaline solution was extracted with ethyl acetate, giving the ester (X; R = Me) (63 mg.), m. p. 174°.

Acid-hydrolysis of the Ester (X; R = Me).—(1) *At room temperature.* The ester (20 mg.) in methanol (1 ml.) and 3N-hydrochloric acid (2 ml.) was set aside for 3 days. The solution was extracted with ethyl acetate and the organic layer was washed with aqueous sodium hydrogen carbonate. The neutral fraction (18 mg.), on recovery, had no significant specific ultraviolet absorption above 240 mμ: crystallisation afforded starting material (16 mg.), m. p. 174°.

(2) *At* 100°. The ester (15 mg.) and 3N-hydrochloric acid (2 ml.) were heated under reflux for 1 hr. The neutral fraction (11 mg.) recovered in ethyl acetate crystallised from light petroleum (b. p. 40—60°) in prisms (7 mg.), m. p. 108—111°, of methyl gibberate [17] (XIII; R = Me; 4bα), identified by mixed m. p. and comparison of the infrared spectra.

Alkaline Hydrolysis of the Ester (X; R = Me).—(*a*) The ester (24·9 mg.) in ethanol (1·5 ml.) and 0·1N-sodium hydroxide (2·80 ml.) was set aside at room temperature for 4 hr. Back-titration with 0·1N-hydrochloric acid (2·11 ml.) showed that 1·0 equiv. of alkali had been consumed. The solution was acidified at 5° to pH 2 and after extraction with ethyl acetate the organic layer was extracted with sodium hydrogen carbonate. The amorphous acid (XII; R = Me, R′ = H) (22 mg.) obtained on recovery (ice-cold solutions [7]) showed no lactone C=O absorption at 1780 cm.$^{-1}$ in dioxan. A portion (9 mg.) was treated with diazomethane, giving the ester (XII; R = R′ = Me) as prisms (5 mg.), m. p. 100—105° (gas evolution), identified by comparison of the infrared spectra.

(*b*) The ester (100 mg.) was heated under reflux for 2 hr. with N-sodium hydroxide (3 ml.), and the cooled solution (at 0°) was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 3 ml.). The foam (85 mg.) obtained on recovery was triturated with ether, giving the amorphous 2,3,7-trihydroxy-1-methyl-8-methylenegibb-4-ene-1,10-dicarboxylic acid [7] (XII; R = R′ = H), m. p. 130—150° (decomp.), identified by comparison of the infrared spectra. Methylation of a portion (60 mg.) furnished the ester (XII; R = R′ = Me) as prisms (38 mg.), m. p. 98—100° (gas evolution), identified as described above.

Action of Alkali on Gibberellic Acid.—(a) *Sodium hydroxide.* Gibberellic acid (35 mg.) in 0·1N-sodium hydroxide (4 ml., 4 equiv.) was kept 18 hr. at room temperature. Back-titration of the cold solution with ice-cold 0·1N-hydrochloric acid showed that 2·04 equiv. of alkali had been consumed. Extraction of the cold acidified solution with ether furnished the acid (XII; R = R′ = H), m. p. 145—155° (decomp.) (11 mg.).

(b) *Ammonia* (By G. W. Elson and Dr. T. P. C. Mulholland). A solution of gibberellic acid (3·0 g.) in 0·1N-ammonia (600 ml.) was kept at room temperature for 6 days, then acidified with hydrochloric acid. Recovery of the product in ethyl acetate gave a gum (2·44 g.). This was extracted with boiling ether (200 ml.), and the extract was concentrated and diluted with light petroleum (b. p. 40—60°), giving a precipitate [1·90 g., $[\alpha]_D^{21}$ +93° (*c* 1·17)]. Fractional precipitation from ether with light petroleum gave, first, fractions with $[\alpha]_D$ +93—100° and, secondly, the *acid* (X; R = H; 1·47 g.) as an amorphous powder, m. p. 150—160°, $[\alpha]_D^{20}$ +104° (*c* 1·12) (Found, dried at 100°: C, 63·2, 62·6; H, 6·65, 6·4. $C_{19}H_{22}O_6.H_2O$ requires C, 62·6; H, 6·6%), $\nu_{max.}$ 3415 (OH); 1755, 1713 cm.$^{-1}$ (C=O); in acetonitrile, 1773, 1739 cm.$^{-1}$. Microhydrogenation resulted in the uptake of 2·0 mol. The acid gave a yellow colour, changing to green and then violet, with concentrated sulphuric acid. The R_F (Whatman No. 1 paper: descending chromatograms at 20°) for the acid (X; R = H) in 4 : 5 : 1 butanol–water–ammonia solution (*d* 0·88) was 0·255 (gibberellic acid, 0·31). This solvent system has been found to give variable results and R_F values for gibberellic acid have been obtained in the range 0·22—0·43; but the relative R_F values for the acid (X; R = H) and gibberellic acid were constant, *viz.*, 0·82 : 1·00.

The methyl ester, prepared with diazomethane, crystallised from ether–light petroleum (b. p. 40—60°) in prisms, m. p. 170—172°, $[\alpha]_D^{23}$ +125° (*c* 1·0), and was identified as the ester (X; R = Me) by mixed m. p. and comparison of the infrared spectra.

Action of Water on the Acid (X; R = H).—The acid (19 mg.) was boiled with water (10 ml.) for 40 hr. On cooling, needles (2 mg.), m. p. 185—195° (softening at 120°), separated; they were identified as allogibberic acid hydrate [12] by the infrared spectrum and mixed m. p. No crystalline products were recovered when the acid (20 mg.) in water (5 ml.) was autoclaved at 15 lb per sq. in. and 121° for 140 min.

Action of Hydrochloric Acid on the Acid (X; R = H).—(*a*) A solution of the acid (25 mg.) in water (16 ml.) was treated at 20° with 3N-hydrochloric acid (8 ml.). No crystals had separated after storage for 5 days at room temperature, followed by 24 hr. at 25°. The mixture was kept at 70—75° for 18 hr. On cooling, gibberic acid [17] (XIII; R = H: 4bα) (9 mg.; m. p. 150—155°) separated.

(*b*) The acid (20 mg.), concentrated hydrochloric acid (0·70 ml.), and water (3·5 ml.) were heated under reflux for 3 hr. The solid {13 mg.; m. p. 160—166°, $[\alpha]_D^{18}$ +5° (*c* 0·9)} which separated on cooling crystallised from ether–light petroleum in needles (8 mg.; m. p. 149—151°) of gibberic acid.

Action of Hydrochloric Acid on the Acid (XII; R = R′ = H).—(a) *At room temperature.* The acid (100 mg.) in 2N-hydrochloric acid (4 ml.) was set aside for 1 week. No precipitate of allogibberic acid was formed (cf. ref. 12) and the solution was continuously extracted with ether. Extraction of the recovered solid with a large volume of boiling toluene gave no allogibberic acid. The toluene-insoluble residue was precipitated by the addition of light petroleum to an ethyl acetate solution and formed an amorphous powder, m. p. 145—180° (decomp.). The infrared spectrum was very similar to, though not quite identical with, that of the acid (XII; R = R′ = H).

(b) *At* 100°. The acid (40 mg.) in water (5 ml.) and concentrated hydrochloric acid (1 ml.) was heated under reflux for 1 hr. Carbon dioxide was evolved and the solution rapidly became cloudy, depositing an oil which solidified. The solid (11 mg.) was collected and crystallised from ethyl acetate–light petroleum as needles (6 mg.), m. p. 145°, not depressed on admixture with gibberic acid. Identity was confirmed by comparison of the infrared spectra.

Acid-hydrolysis of the Ester (XII; R = R′ = Me).—(a) *At room temperature.* The ester (0·5 mg.) in ethanol (1 drop) and 0·1N-hydrochloric (2 ml.) was set aside at room temperature for 200 hr. and the ultraviolet absorption was determined at intervals. There was no significant increase in $E^{1\%}_{1\,cm.}$ at 254 or 270 mμ.

(b) *At* 100°. The ester (10 mg.) was heated under reflux for 30 min. with 3N-hydrochloric acid (1 ml.). The oil which separated during the reaction was extracted with ethyl acetate. Recovery, after washing with aqueous sodium hydrogen carbonate, gave a yellow gum (7 mg.) which crystallised from methanol in needles (1 mg.), m. p. 188—195°, of the triene (XVI) (see below). The mother-liquors showed $\lambda_{max.}$ 242 mμ in addition to bands, due to the triene (XVI), at 278, 287, and 310 mμ.

Action of Methanolic Hydrogen Chloride on Methyl Gibberellate and on the Ester (X; R = Me).—(*a*) Methyl gibberellate (300 mg.) in methanol (4 ml.) was saturated with dry hydrogen chloride and then heated under reflux for 1 hr. in a slow stream of hydrogen chloride. The yellow solution was cooled, then poured over crushed ice (10 g.), and the resulting mixture was immediately extracted with ether. The ether extract was washed with aqueous sodium hydrogen carbonate, and the neutral fraction, a gummy solid (221 mg.), was recovered and chromatographed on alumina (10 × 1·5 cm.) in benzene–light petroleum (1 : 1; 50 ml.). Elution of the column in ultraviolet light gave the following fractions: (i) Benzene–light petroleum (1 : 1; 800 ml.) removed a non-fluorescent band and afforded a gum (18 mg.) which crystallised from light petroleum (b. p. 40—60°) in needles (5 mg.), m. p. 96°, of methyl epigibberate [17] (XIII; R = Me; 4bβ), identified by mixed m. p. and comparison of the infrared spectra. (ii) Benzene–light petroleum (1 : 1; 400 ml.) removed a blue-fluorescent band, giving a gum (38 mg.). Crystallisation from light petroleum afforded needles (5 mg.), m. p. 109°, of methyl gibberate, identified as described above. (iii) Benzene–light petroleum (1 : 1; 400 ml.) gave, from a yellow-fluorescent band, an intractable yellow gum (29 mg.), $\lambda_{max.}$ 242 mμ. (iv) Benzene–methanol (200 : 1; 300 ml.) removed a yellow band, giving a yellow solid (92 mg.) (see below). (v) Benzene–methanol (100 : 1 and 50 : 1; 200 ml. each), from a diffuse blue-flourescent band, gave an intractable gum (31 mg.).

Fraction (iv) was recrystallised three times from light petroleum (with losses) and formed needles (62 mg.), m. p. 197—198°, $[\alpha]_D^{19}$ +762° (*c* 0·5 in acetone) of *methyl* 1,7-*dimethyl*-8-*oxo*-7α-*gibba*-3,4a(4b),5-*triene*-1,10-*dicarboxylate* (XVI) (Found: C, 70·4, 70·8; H, 6·8, 6·9; OMe, 17·4. $C_{21}H_{24}O_5$ requires C, 70·8; H, 6·8; 2OMe, 17·4%), $\lambda_{max.}$ ~275, 287, 310 mμ (log ε 4·32, 4·42, 4·27 respectively), $\nu_{max.}$ (OH absent) 1736 cm.$^{-1}$ (C=O); in chloroform 1737 cm.$^{-1}$ (broad); [*M*] (500 mμ) +2800°, (400 mμ) +11,000°, (350 mμ) +34,000°, (330 mμ) +72,000°, (320 mμ) +160,000°. Microhydrogenation led to the uptake of 2·12 mol. The triene gave an intense blue colour with concentrated sulphuric acid.

The *oxime*, prepared by heating the triene (25 mg.) under reflux with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol for 18 hr., formed a microcrystalline powder (12 mg.), m. p. 146—152° (decomp.), from light petroleum (Found: N, 3·7. $C_{21}H_{25}O_5N$ requires N, 3·8%), $\lambda_{max.}$ ~280, 290, ~305 mμ (log ε 4·35, 4·50, 4·30 respectively), $\nu_{max.}$ 3560, 3440, 3250 (OH); 1728 (C=O); 1634 cm.$^{-1}$ (C=N).

No triene (XVI) was obtained when the reaction time was reduced to 0·25 hr.; and a significantly lower yield resulted after 2 hr.

(*b*) The ester (X; R = Me) (220 mg.) in methanol (5 ml.) was treated with hydrogen chloride as described in (*a*), and the neutral product (180 mg.) was chromatographed in the same manner

giving the following fractions: (i) Benzene–light petroleum (1 : 1; 100 ml.), from a non-fluorescent band gave a gum (18 mg.) which yielded methyl epigibberate (2 mg.) on crystallisation from light petroleum. (ii) Benzene–light petroleum (1 : 1; 100 ml.) (blue-fluorescent band) gave methyl gibberate (10 mg. from 24 mg. of gum). (iii) Benzene–light petroleum (1 : 1; 50 ml.), removed a blue-fluorescent band (12 mg.), (iv) benzene–light petroleum (1 : 1; 150 ml.) a yellow band (17 mg.), and (v) benzene (30 ml.) a yellow band (9 mg.), these materials being intractable. (vi) Benzene (220 ml.), from a blue-fluorescent band, gave a yellow gum (50 mg.), whence extraction with light petroleum followed by sublimation at 160°/10^{-4} mm. furnished a yellow amorphous solid, m. p. <100°, $\lambda_{max.}$ 242 mμ ($E^{1\%}_{1\,cm.}$ 310), ketonic to Brady's reagent. (vii) Benzene–methanol (200 : 1; 100 ml.) gave a yellow solid (53 mg.), whence the triene (XVI) (19 mg.), m. p. 190—192°, was isolated.

Action of Acid on Methyl Gibberellenate.—The ester [10] (15 mg.) was heated under reflux for 20 min. with 3N-hydrochloric acid (1 ml.). The yellow gum which separated was extracted with ethyl acetate, and the extract was washed with sodium hydrogen carbonate solution. The neutral product (10 mg.) recovered was chromatographed in benzene (5 ml.) on alumina (8 × 0·5 cm.) in ultraviolet light. The following fractions were obtained: (i) A pale blue-fluorescent band gave to benzene (25 ml.) an oil (1 mg.), $\lambda_{max.}$ 257 mμ (unchanged methyl gibberellenate). (ii) Benzene–ether (5 : 1; 10 ml.), from a blue-fluorescent band, gave a yellow gum (2 mg.), $\lambda_{max.}$ 242 mμ. (iii) Benzene–ether (5 : 1; 150 ml.), from a yellow band, gave a solid (5 mg.), crystallising from methanol in needles (2 mg.), $\lambda_{max.}$ 287, 310 mμ, of the triene (XVI). The remaining fractions, eluted with benzene–methanol (200 : 1; 150 ml.), were intractable.

Dehydrogenation of the Triene (XVI).—The triene (116 mg.) and powdered selenium (116 mg.) were heated in a slow current of nitrogen for 6 hr. at 360°. The product (32 mg.), recovered by ether-extraction, was chromatographed on alumina (15 × 1·8 cm.) in light petroleum (b. p. 40—60°). Elution with light petroleum (b. p. 40—60°) (550 ml.) gave a semi-solid fraction (10 mg.) which furnished 1,7-dimethylfluorene,[20] identified by mixed m. p. and comparison of the infrared spectra, on recrystallisation from methanol.

Reduction of the Triene (XVI).—(a) *Catalytic reduction.* The triene (118 mg.) in ethyl acetate (25 ml.) in presence of 10% palladium–charcoal (118 mg.) took up 18 ml. of hydrogen (2·4 mol.). The product crystallised from ethyl acetate–light petroleum in needles (76 mg.), m. p. 127—128°, $[\alpha]_D^{17}$ +24° (*c* 0·4), of *methyl* 1,7-*dimethyl*-8-*oxo*-7α-*gibb*-4a(4b)-*ene*-1,10-*dicarboxylate* (XXIV) (Found: C, 69·8; H, 8·1. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·8%), $\lambda_{max.}$ 204 mμ (log ε 4·06), $\nu_{max.}$ (OH absent) 1742 cm.$^{-1}$ (C=O). It gave no colour with concentrated sulphuric acid and was ketonic to Brady's reagent.

(b) *Reduction with sodium borohydride.* The triene (100 mg.) in methanol (20 ml.) at 10° was stirred for 1 hr. during the addition of sodium borohydride (100 mg.) in methanol (5 ml.). Excess of hydride was decomposed by the addition of acetic acid, and the solution was concentrated *in vacuo* to small bulk. After the addition of water the oily product (95 mg.) was extracted with ethyl acetate and crystallised from ethyl acetate–light petroleum in prisms (43 mg.), m. p. 149—153°, of *methyl* 8ξ-*hydroxy*-1,7-*dimethyl*-7α-*gibba*-3,4a(4b),5-*triene*-1,10-*dicarboxylate* (XXIII) (Found: C, 69·6; H, 7·6; OMe, 17·2. $C_{21}H_{26}O_5$ requires C, 70·4; H, 7·3; 2OMe, 17·3%), $\lambda_{max.}$ ~275, 286, ~296 mμ (log ε 4·38, 4·49, 4·40 respectively), $\nu_{max.}$ 3560 (OH); 1728 cm.$^{-1}$ (C=O). It gave an intense green colour with concentrated sulphuric acid.

Hydrogenolysis of Methyl Gibberellate and of the Ester (X; R = Me).—(*a*) (With Dr. T. P. C. Mulholland). Methyl gibberellate (500 mg.) in acetic acid (50 ml.) was added to Adams platinum oxide (200 mg.), previously reduced with hydrogen in acetic acid (20 ml.), and hydrogenated to completion (uptake *ca.* 2·9 mol. in 2 hr.). After removal of the solvent *in vacuo* the gummy product was separated into neutral (200 mg.) and acidic (305 mg.) fractions in the usual way. The neutral fraction crystallised from aqueous methanol in prisms, m. p. 242—245°, of mixed methyl tetrahydrogibberellates (8-epimers).[7] The acid fraction was recrystallised three times from ethyl acetate, giving prisms (96 mg.), m. p. 269—271° (decomp.; after previous softening) of *methyl* 1-*carboxy*-2,7-*dihydroxy*-1,8-*epi*-*dimethylgibbane*-10-*carboxylate* (XV) (Found: C, 65·2; H, 8·45. $C_{20}H_{30}O_6$ requires C, 65·55; H, 8·25%), $\nu_{max.}$ 3410, ~2650—2500 (broad) (OH); 1741, 1715 cm.$^{-1}$ (C=O); in dioxan, no band near 1780 cm.$^{-1}$ (γ-lactone C=O).

(*b*) The ester (X; R = Me) (500 mg.) in acetic acid (50 ml.) was subjected to hydrogenolysis in the presence of a reduced Adams platinum oxide catalyst (200 mg.) as described in (*a*) above.

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The neutral fraction (27 mg.) was rejected and the acid fraction (459 mg.) recrystallised from ethyl acetate as before, giving the acid (XV) (110 mg.), m. p. 266—268° (decomp., after previous softening), identified by comparison of the infrared spectra.

Hydrogenation of the Ester (X; R = Me).—The ester (250 mg.) in ethyl acetate (50 ml.) was hydrogenated at room temperature in the presence of 10% palladium–charcoal (50 mg.) until 1·1 mol. had been taken up. The gummy product was separated into neutral (206 mg.) and intractable acidic (40 mg.) fractions by extraction with aqueous sodium hydrogen carbonate and recovery. The neutral fraction in benzene–methanol (200 : 1; 100 ml.) was chromatographed on alumina (14 × 1 cm.). Elution with the same solvent (volumes in parentheses) gave the following gummy fractions which crystallised from ethyl acetate–light petroleum: (i) (800 ml.; 120 mg.) prisms, m. p. 223—228°, (ii) (400 ml.; 55 mg.) intractable mixtures, (iii) (400 ml.; 28 mg.) needles, m. p. 164—166°. Fraction (i) was recrystallised three times from ethyl acetate, giving *methyl* 1-*carboxy*-2(ax),3,7-*trihydroxy*-1,8-*epi*-*dimethylgibb*-4-*ene*-10-*carboxylate* 1 ⟶ 3-*lactone* (XXV) as prisms (40 mg.), m. p. 232—235°, $[\alpha]_D^{24}$ +84° (*c* 0·5) (Found: C, 66·4; H, 7·2. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%), $\nu_{max.}$ 3485, 3360 (OH); 1741 (C=O); 1682 cm.$^{-1}$ (C=C). Fraction (iii) crystallised from ethyl acetate–light petroleum in needles or plates (16 mg.), m. p. 171—172°, $[\alpha]_D^{24}$ +112° (*c* 0·5), of *methyl* 1-*carboxy*-2(ax),3,7-*trihydroxy*-1,8-*dimethylgibb*-4-*ene*-10-*carboxylate* 1 ⟶ 3-*lactone* (XXV) (Found: C, 66·4; H, 7·5%), $\nu_{max.}$ (needle form) 3410 (broad) (OH); 1762 (broad), 1736 (C=O); 1676 cm.$^{-1}$ (C=C); (plate form) 3470, 3300; 1770, 1730; 1675 cm.$^{-1}$.

Both epimers gave intense reddish-purple colours with concentrated sulphuric acid.

Repetition of this reduction gave erratic yields of crude neutral products: on one occasion the weights of the acidic and neutral fractions were 116 mg. and 130 mg. respectively and the weights of the epimers, m. p. 232—235° and 171—172°, isolated by chromatography, were 26 and 8 mg. respectively. When the catalyst : ester ratio was increased to 1 : 1, the yield of neutral fraction was very considerably reduced and the weight of acidic material was correspondingly increased.

Ozonolysis of the Ester (X; R = Me).—(a) *In ethyl acetate at* −70°. Ozonised oxygen equivalent to 1·0 mol. of ozone was passed through the ester (3·6 g.) in ethyl acetate (200 ml.) at −70°. The ethyl acetate was removed *in vacuo* at 20° and the residual gum was decomposed with water (200 ml.) during 3—4 days. Needles (195 mg.), m. p. 96—115° (*A*), separated and were filtered off. The aqueous solution was extracted with ethyl acetate, and the product was separated into acidic (1·12 g. of gum) and neutral (2·19 g.) fractions as usual. The neutral fraction was separated by treatment with Girard's reagent P into a non-ketonic portion (829 mg.), which yielded unchanged ester (X; R = Me), m. p. 172°, on crystallisation from ethyl acetate–light petroleum, and a ketonic gum (667 mg.).

The latter was chromatographed on alumina (20 × 2 cm.) in light petroleum (b. p. 40—60°) containing a little ethyl acetate. A series of intractable gums (55 mg.) were eluted with various solvents. Benzene–methanol (100 : 1; 800 ml.) then eluted a solid (185 mg.) which crystallised from ethyl acetate in prisms (79 mg.), m. p. 236—241°, of *methyl* 1-*carboxy*-4,4a-*epoxy*-2(ax),3,7-*trihydroxy*-1-*methyl*-8-*oxogibbane*-10-*carboxylate* 1 ⟶ 3-*lactone* (Found: C, 60·7; 60·4; H, 5·9, 6·0. $C_{19}H_{22}O_8$ requires C, 60·3; H, 5·9%), $\nu_{max.}$ 3425 (OH); 1778, 1738, 1722 cm.$^{-1}$ (C=O); in acetonitrile, 1786, 1755, 1737 cm.$^{-1}$. It gave a yellow colour with a green fluorescence with concentrated sulphuric acid and reduced ammoniacal silver nitrate on warming.

Further elution of the column with benzene–methanol (50 : 1; 100 ml.) furnished *methyl* 1-*carboxy*-2(ax),3,7-*trihydroxy*-1-*methyl*-8-*oxogibb*-4-*ene*-10-*carboxylate* 1 ⟶ 3-*lactone* (XI; R = R′ = H), needles (32 mg.), m. p. 175—177° (Found: C, 62·8; H, 6·3. $C_{19}H_{22}O_7$ requires C, 63·0; H, 6·1%), $\nu_{max.}$ 3401 (broad) (OH); 1779, 1754, 1724 (C=O); 1678 cm.$^{-1}$ (C=C). Recrystallisation from ethyl acetate–light petroleum gave the *hemihydrate*, needles, double m. p. 118—120° (gas evolution) and 175—177° (Found: C, 61·6, 61·35; H, 6·4, 6·4. $C_{19}H_{22}O_7,0{\cdot}5H_2O$ requires C, 61·4; H, 6·2%), $\nu_{max.}$ 3500, 3405, ~3285, ~3160 (OH); 1780, 1756, 1731 (C=O); 1678 cm.$^{-1}$ (C=C); in chloroform, 3615, 1777, 1755, 1736 cm.$^{-1}$. The anhydrous ketol (XI; R = R′ = H) was obtained by drying the hemihydrate *in vacuo* at 150°/0·005 mm.

The hemihydrate (49 mg.) was also obtained in the next eluate [benzene–methanol (50 : 1; 100 ml.)] from the column. Continued elution with the same eluant (700 ml.) gave a solid (270 mg.) which crystallised from ethyl acetate–light petroleum in needles (142 mg.), m. p. 104—106°, of the *ketol* (XI; R = R′ = H) *hydrate* (Found: C, 60·6; H, 6·45. $C_{19}H_{22}O_7,H_2O$ requires C, 60·0; H, 6·4%), $\nu_{max.}$ 3560, 3430, 3320 (OH); 1750 (broad), 1727 (C=O); 1677 (C=C);

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1635 (broad) cm.$^{-1}$ (H_2O); in acetonitrile 1769, 1754, 1732, 1674 cm.$^{-1}$, [*M*], positive Cotton effect curve (330 mμ, peak) +5050°, (282, trough) −2820°. The infrared solution spectra of the ketol (XI; R = R′ = H) and its hemihydrate and hydrate were identical. The compounds gave red colours with concentrated sulphuric acid and reduced ammoniacal silver nitrate on warming.

The *diacetate* (XI; R = R′ = Ac) prepared with acetic anhydride in pyridine at room temperature during 3 days was an amorphous powder, m. p. 115—125° (Found: C, 61·7; H, 6·4. $C_{23}H_{26}O_9$ requires C, 61·9; H, 5·9%), $\nu_{max.}$ OH absent; 1767, 1734 (C=O); 1673 cm.$^{-1}$ (C=C).

The acid fraction crystallised from ethyl acetate in prisms (220 mg.), m. p. 176—178°, $[\alpha]_D^{22}$ +52° (*c* 1·0), of 1-*carboxy*-1,2,3,5,6,7,8,10,12α,13-*decahydro*-2,3-*dihydroxy*-9β-*methoxycarbonyl*-1-*methyl*-7-*oxo*-8aβ-*fluorenylacetic acid* 1 ⟶ 3-*lactone* (XIV; R = H) (Found: C, 60·7; H, 5·7; OMe, 9·0. $C_{19}H_{22}O_8$ requires C, 60·3; H, 5·9; OMe, 8·2%), $\nu_{max.}$ 3400, 3345 (OH); 1776, 1753, 1735, and 1711 (C=O); ~1680 cm.$^{-1}$ (C=C). It gave an orange colour with concentrated sulphuric acid.

The *methyl ester* (XIV; R = Me), prepared with diazomethane, was a glass which softened below 90° and distilled at 140—160° (bath)/4·7 × 10^{-3} mm. (Found: C, 61·0; H, 6·4. $C_{20}H_{24}O_8$ requires C, 61·2; H, 6·2%), $\nu_{max.}$ 3410 (OH); 1769, 1733 (broad) cm.$^{-1}$ (C=O). It gave a deep yellow colour with concentrated sulphuric acid.

The residue (820 mg.) from the mother-liquors, after the acid (XIV; R = H) had been filtered off, was methylated in methanol (5 ml.) with ethereal diazomethane, and the gummy product was chromatographed on alumina (30 × 2 cm.). The following fractions were eluted (all gums): (i) benzene (100 ml.) and benzene–methanol (400 : 1; 200 ml.) gave 145 mg.; (ii) benzene–methanol (200 : 1; 600 ml.) gave 66 mg.; (iii) benzene–methanol (100 : 1; 900 ml.) afforded the ester (XIV; R = Me) (563 mg.), identified after distillation at 140—160°/5 × 10^{-3} mm. by comparison of the infrared spectra.

Fractions (i) and (ii) crystallised from ethyl acetate–light petroleum in needles (110 mg.), m. p. 202—204°, $[\alpha]_D^{18}$ +8° (*c* 0·77 in acetone) of *methyl* 1-*carboxy*-4,11-*epoxyperhydro*-2,3-*dihydroxy*-9β-*methoxycarbonyl*-1-*methyl*-7-*oxo*-13β-*fluorenylacetate* 1 ⟶ 3-*lactone* (Found: C, 58·8; H, 6·1; OMe, 15·2. $C_{20}H_{24}O_9$ requires C, 58·8; H, 5·9; 2OMe, 15·2%), $\nu_{max.}$ 3515 (OH); 1773, 1738, 1715 cm.$^{-1}$ (C=O); in chloroform, 3455, 1786, 1737, 1722 cm.$^{-1}$. At 205, 210, 220, and 230 mμ ε was 1130, 1000, 700, and 340, respectively. There was no uptake of hydrogen on microhydrogenation. The ester gave a yellow colour with a green fluorescence with concentrated sulphuric acid.

The *acetate*, prepared with acetic anhydride in pyridine at room temperature during 20 hr., crystallised from ethyl acetate–light petroleum in needles, m. p. 228—229° (Found: C, 58·5; H, 5·9; Ac, 8·9. $C_{22}H_{26}O_{10}$ requires C, 58·7; H, 5·8; 1Ac, 9·3%), $\nu_{max.}$ (no OH absorption) 1783, 1749, 1730, 1716 cm.$^{-1}$ (C=O).

The solid (*A*) crystallised from aqueous methanol in needles (90 mg.), m. p. 206—208°, of a *substance* (Found: C, 61·1; H, 6·7. $C_{19}H_{22}O_7$,CH_3·OH requires C, 60·9; H, 6·6%), $\nu_{max.}$ 3555, 3495, 3410 (sh), 3320, 3125 (OH); 1788, 1710 (C=O); 1681, 1670 (sh) (C=C); in chloroform, 1796, 1732 cm.$^{-1}$. Solvent-free material was obtained on drying at 60° *in vacuo* (Found: C, 63·15; H, 6·3; OMe, 8·35. $C_{19}H_{22}O_7$ requires C, 63·0; H, 6·1; OMe, 8·6%) and had $\nu_{max.}$ 3635, 3540, 3120 (sh) (OH); 1782, 1723 (C=O); 1659 cm.$^{-1}$ (C=C). It gave an intense red colour with concentrated sulphuric acid.

(b) *In acetic acid at* 20°. Ozonised oxygen was passed through the ester (1·0 g.) in acetic acid (40 ml.) at 20° (uptake 1 mol.). After 1 hr. the mixture was steam-distilled. Treatment of the distillate with saturated aqueous dimedone gave the formaldehyde derivative (39%), m. p. and mixed m. p. 187—189°. The non-steam volatile residue was made alkaline by the addition of sodium carbonate and was extracted with ethyl acetate, giving a neutral fraction (620 mg.). The aqueous layer was then adjusted to pH 2 by addition of concentrated hydrochloric acid and was re-extracted with ethyl acetate, giving an acid fraction (350 mg.). The neutral fraction was chromatographed on alumina (40 × 2 cm.), and the column was eluted as described in (a) above. After a series of intractable gums had been eluted, benzene–methanol (100 : 1; 850 ml.) brought off a gum (120 mg.) which crystallised from ethyl acetate–light petroleum in felted needles (12 mg.) of the *ketol acetate* (XI; R = H, R′ = Ac), m. p. 173—174° (Found: C, 62·45; H, 6·1. $C_{21}H_{24}O_8$ requires C, 62·4; H, 6·0%), $\nu_{max.}$ 3430 (OH); 1759, 1738 (C=O); 1675 cm.$^{-1}$ (C=C); in acetonitrile, 1769, 1738 cm.$^{-1}$. It gave a claret colour with

concentrated sulphuric acid and was recovered after attempted oxidation with sodium metaperiodate in aqueous methanol. Acetylation gave the amorphous diacetate (XI; R = R′ = Ac), m. p. 115—125°, identified by the infrared spectrum.

Continued elution of the column with benzene–methanol (100 : 1; 800 ml.) gave a gum (157 mg.) which furnished the hydrate (26 mg.), double m. p. 102—106° and 172°, of the ester (X; R = Me). Benzene–methanol (50 : 1; 2·1 l.) then eluted a series of solid fractions (198 mg.) which gave the hemihydrate and hydrate of the ketol (XI; R = R′ = H) on recrystallisation from ethyl acetate–light petroleum.

The acid fraction was methylated and the product was chromatographed as described in (a) above. After intractable gummy fractions of 43 mg. had been eluted [benzene (400 ml.) and benzene–methanol (100 : 1; 700 ml.)], benzene–methanol (50 : 1; 600 ml.) furnished the ester (XIV; R = Me) (210 mg.), identified after distillation *in vacuo* by comparison of the infrared spectra.

Oxidation of the Ketol (XI; R = R′ = H).—(a) *With sodium periodate.* The ketol hydrate (27 mg.) in methanol (2 ml.) and water (1 ml.) containing sodium metaperiodate (30 mg.) was set aside at room temperature for 22 hr. The methanol was distilled off *in vacuo* and the residue was diluted with water and acidified to pH 3 with concentrated hydrochloric acid. Extraction with ethyl acetate was followed by separation into neutral (2 mg.) and acidic (22 mg.) fractions. The acid fraction was methylated with diazomethane and the product was chromatographed on alumina (7 × 1 cm.) as described above. Benzene–methanol (100 : 1) eluted a glass which after distillation at 140—160°/5 × 10^{-3} mm. was identified as the ester (XIV; R = Me) by the infrared spectrum.

(b) *With perbenzoic acid.* The ketol hydrate (32 mg.) in chloroform (1 ml.) was added to perbenzoic acid (14 mg., 1·2 mol.) in chloroform (1 ml.) at 0° and set aside at room temperature for 48 hr., then washed with sodium hydrogen carbonate. Evaporation gave a gum (22 mg.) which crystallised from ethyl acetate in prisms, m. p. 233—237° (10 mg.), of the ketol (m. p. 236—241°), identified by comparison of the infrared spectra.

Acid-hydrolysis of the Acid (XIV; R = H) *and its Ester* (XIV; R = Me).—(*a*) The acid (20 mg.) was heated under reflux for 1 hr. with 3N-hydrochloric acid (2 ml.). Extraction of the cooled solution with ethyl acetate afforded an intractable gum which was methylated with diazomethane. The product crystallised from ethyl acetate in prisms (2 mg.), m. p. 202—204°, of the ester[1] (XVII), identified by mixed m. p. and comparison of the infrared spectra.

(*b*) The ester (34 mg.) in methanol (1 ml.) and 3N-hydrochloric acid (8 ml.) was heated under reflux for 30 min. The neutral product (30 mg.), recovered in ethyl acetate, crystallised from ethyl acetate–light petroleum in prisms (10 mg.), m. p. 200—203°, of the ester (XVII), identified as before.

Oxidation of the Ketol, m. p. 236—241°.—The ketol (10 mg.) in methanol (1 ml.) and water (3 ml.) containing sodium metaperiodate (15 mg.) was set aside at room temperature for 20 hr. The product was worked up as described for the ketol (XI; R = R′ = H) and separated into neutral (3 mg.) and acid (7 mg.) fractions. Methylation of the acid fraction gave prisms (4 mg.) of the ester $C_{20}H_{24}O_8$, m. p. 202—204°, identified by comparison of the infrared spectra.

Attempted Acid-hydrolysis of the Ester, m. p. 202—204°.—The ester (30 mg.) in methanol (5 ml.) and 3N-hydrochloric acid (5 ml.) was heated under reflux for 30 min. After removal of the methanol *in vacuo* the product was recovered in ethyl acetate and separated into neutral (10 mg.) and acidic (110 mg.) fractions. The neutral fraction deposited unchanged starting material (2 mg.) on crystallisation from ethyl acetate–light petroleum. The acid fraction was an intractable gum which showed no specific absorption band near 270 mμ.

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483. *Interdependence of Molecular Conformation and Conjugation in Aromatic Ethers. Part IV.**

By G. Baddeley and N. H. P. Smith.

The ultraviolet absorption spectra and rates of bromination of veratrole and the diethers *o*-$\overline{O\cdot C_6H_4\cdot O\cdot[CH_2]_n}$, *i.e.*, (III) where n is 1, 2, 3, and 5, and the rates of solvolysis of their chloromethyl derivatives in 90% aqueous ethanol have been determined and compared with the corresponding data for methyl *o*-tolyl ether and the ethers *o*-$\overline{CH_2\cdot C_6H_4\cdot O\cdot[CH_2]_n}$, *i.e.*, (I; X = H) where n = 1, 2, and 3, and their chloromethyl derivatives. The order of decreasing reactivity for diethers is (IV) > (III; n = 1) > (III; n = 2) > (III; n = 3) whereas that for the monoethers is (I; n = 1) ⩾ (I; n = 2) ⩾ (II) ⩾ (I; n = 3). The differences between these two series are qualitatively interpreted by superimposing inductive effects caused by interaction of the oxygen atoms in the diethers (III) through the methylene chain which joins them and conformational effects provided by the size of the heterocycles.

In Part I,[1] the ultraviolet absorption spectra and rates of bromination of the ethers (I; X = H, n = 1—3) and the rates of unimolecular solvolysis of their chloromethyl derivatives (I; X = CH_2Cl) were compared with those of anisole and methyl *o*-tolyl ether (II; X = H) and their corresponding chloromethyl derivatives (see II; X = CH_2Cl). In brief, relative to methyl *o*-tolyl ether, coumaran and chroman were shown to be highly reactive while homochroman has a low reactivity. These differences were explained on the basis that the five- and six-membered heterocycles in (I; n = 1 and 2, respectively) enforce a degree of coplanarity and near-coplanarity of the ether group and the benzene ring which is greater than that in methyl *o*-tolyl ether, while the seven-membered heterocycle in (I; n = 3) has the opposite effect. Similar conformational effects must be expected to influence the absorption spectra and rates of bromination of the diethers (III; X = H, n = 1—3) and the rates of solvolysis of their chloromethyl derivatives (III; X = CH_2Cl). The corresponding data for veratrole and its chloromethyl derivative (IV; X = H and CH_2Cl, respectively) are the appropriate basis for the comparison which is now provided. The data for 3,9-dioxa-1,2-benzocyclononene (III; n = 5) are also included.

Table 1. *Constants of the Arrhenius equation, $k = Ae^{-E/RT}$, for the formation of hydrogen chloride by the solvolysis of the substituted benzyl chlorides in 90% aqueous ethanol.*

No.	Substituents	$10^4k_{0\cdot0}$ (min.$^{-1}$)	$10^4k_{25\cdot0}$ (min.$^{-1}$)	$10^4k_{45\cdot0}$ (min.$^{-1}$)	E (kcal./mole)	$10^{-11}A$ (min.$^{-1}$)
1	3,4-$(MeO)_2$	12·6	255		19·6	46·6
2	3,4-O·CH_2·O		42·4	352	20·1	17·3
3	3,4-O·$[CH_2]_2$·O		24·3	212	20·5	21·8
4	3,4-O·$[CH_2]_3$·O		4·18	37·2	20·7	5·2
5	3,4-O·$[CH_2]_5$·O		29·3	243	20·0	8·7

The rate coefficients for the unimolecular solvolysis of the chloromethyl derivatives in 90% aqueous ethanol (see Part I) are listed in Table I, while Table 2 provides a comparison of these solvolyses with those of the chloromethyl derivatives of the monoethers (I; X = CH_2Cl).

* Part III, *J.*, 1958, 4665.

[1] Baddeley, Smith, and Vickars, *J.*, 1956, 2455.

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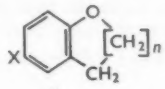
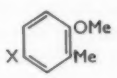
TABLE 2. *Comparison of energies of activation and rates of solvolysis at 25° of the chlorides* (I, II, III, *and* IV; X = CH_2Cl).

Chlorides (III) and (IV) (X = CH_2Cl)	$10^4k_{25\cdot0}$ (min.$^{-1}$)	*E* (kcal./mole)	*E* (kcal./mole)	$10^4k_{25\cdot0}$ (min.$^{-1}$)	Chlorides (I) and (II) (X = CH_2Cl)
(IV)	255	19·6	19·6	510	(II)
(III; *n* = 1)	42·4	20·1	17·3	3630	(I; *n* = 1)
(III; *n* = 2)	24·3	20·5	18·8	1060	(I; *n* = 2)
(III; *n* = 3)	4·18	20·7	21·0	18·5	(I; *n* = 3)
(III; *n* = 5)	29·3	20·0	20·6	130	*p*-MeO·C_6H_4·CH_2Cl


(I)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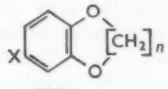
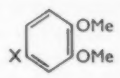

(III)


(IV)

The comparison of the solvolyses of the chloromethyl derivatives of the diethers (III; *n* = 1—3) with those of the monoethers (I; *n* = 1—3) shows that while reactivity in both series falls with increase in *n*, in accordance with the expected influence of change in the value of *n* on the conformational relation of ether group to benzene ring, the fall (as 10 : 6 : 1) in the former series is much less than that (195 : 57 : 1) in the latter. Further, whereas the chloromethyl derivatives of the monoethers (I; *n* = 1 and 2) are more reactive than the chloromethyl derivative of methyl *o*-tolyl ether (II) by factors of 7 and 2, respectively, those of the diethers (III; *n* = 1 and 2) are less reactive than that of veratrole (IV) by factors of 6 and 10·5, respectively. Similar differences between the two series, shown by the relative rates of bromination which, together with the wavelengths and extinction coefficients for the middle of the three peaks in the region 2500—3000 Å, are listed in Table 3:

TABLE 3. *Comparison of the ultraviolet absorption spectra and relative rates of bromination of the ethers* (I, II, III, *and* IV; X = H).

Diethers (III) and (IV) (X = H)	$k_{rel.}$	λ	ε	ε	λ	$k_{rel.}$	*Ethers* (I) and (II) (X = H)
(IV)	1·31	2770	2336	1810	2720	1·00	(II)
(III; *n* = 1)	0·0178	2840	3122	3090	2810	13·7	(I; *n* = 1)
(III; *n* = 2)	0·0169	2780	2340	2125	2760	4·9	(I; *n* = 2)
(III; *n* = 3)	0·00746	2750	1360	678	2670	0·219	(I; *n* = 3)
(III; *n* = 5)	6·8	2750	1322	1575	2710	0·148	C_6H_5·OMe

In both series, change of *n* from 1 to 2 to 3 decreases the rate of bromination, but whereas this change in *n* in the series of monoethers (I) provides a rate ratio of 62 : 22 : 1, in the diethers (III) it gives only 2·4 : 2·3 : 1. Again, whereas the ethers (I; *n* = 1 and 2) are *more* reactive than methyl *o*-tolyl ether by factors 13·7 and 4·9, respectively, the diethers (III; *n* = 1 and 2) are *less* reactive than veratrole by factors of 74 and 77, respectively. These differences in variation in chemical reactivity in the two series can be qualitatively interpreted in terms of inductive interaction of the oxygen atoms in the diethers through the methylene group or groups which bridge them. This inductive interaction in the compounds (III), which is greatest when *n* is 1 and decreases rapidly with increase in *n* to 2 and 3, opposes electromeric release of electrons from ether oxygen atom to benzene ring and thereby hinders bromination of the diethers (III; X = H) and unimolecular solvolysis of their chloromethyl derivatives. Thus, whereas conformational differences alone would provide relative reactivities similar to those observed for the ethers (I and II) and their chloromethyl derivatives, *i.e.*, (III; *n* = 1) ⩾ (III; *n* = 2) ⩾ (IV) ⩾ (III; *n* = 3), the inductive interaction alone would give (IV) > (III; *n* = 3) > (III; *n* = 2) ⩾ (III; *n* = 1). The observed sequence of reactivities (IV) > (III; *n* = 1) > (III;

$n = 2$) > (III; $n = 3$) can, therefore, be qualitatively interpreted by superimposing these conformational and inductive effects. Part V will be concerned with measuring these inductive effects and will enable the conformational influences in the diethers (III) to be compared with those in the ethers (I).

A decrease in conjugation results in a shorter wavelength and a smaller coefficient of absorption. Thus the spectroscopic data in Table 3 show the conformational influences on conjugation in the diethers to be similar to those in the monoethers. Compounds (I and III; $n = 2$) have very similar absorption bands, $\lambda = 2760$ and 2780 ($\varepsilon = 2125$ and 2340, respectively). In each series of compounds, the change in the value of n from 2 to 1 increases, and by about the same amount in each series, both the wavelength and extinction coefficient of absorption while the change of n from 2 to 3 lowers both the wavelength and coefficient of absorption. This fall in the value of λ and ε for the monoethers is, however, greater than that for the diethers.

In conclusion it should be remarked that the data now provided (see Tables 2 and 3) show veratrole to be nine times more reactive than anisole in bromination, and its chloromethyl derivative to be twice as reactive as 4-methoxybenzyl chloride in solvolysis. Since a *meta*-methoxyl group withdraws electrons, *e.g.*, 3-methoxy-αα-dimethylbenzyl chloride in 90% aqueous acetone at 25° is solvolysed only half as readily as isopropyl chloride,[2] the present comparison is best explained by the assumption we made in 1951[3] that a 3-methoxyl group facilitates electron release from a 4-methoxyl group by a process of electrostatic interaction (see V) which other authors, concerned with other anomalies, have called (V) "built-in solvation." In our instance it requires the methyl group of the 3-methoxyl group to be oriented away from the 4-methoxyl group. This conformational relationship of the two ether groups is possible also in the heterocyclic diether (III; $n = 5$) and may be the cause of the unexpectedly high reactivity of this diether and of its chloromethyl derivative in the bromination and solvolysis, respectively.

Experimental

Diethers.—Veratrole, m. p. 22·0—22·5°,[4] 1,3-dioxaindane,[5] b. p. 172—173°, 1,4-dioxatetralin,[6] b. p. 82—83°/6 mm., 3,7-dioxa-1,2-benzocycloheptene,[7] b. p. 107—108°/15 mm. (Found: C, 72·0; H, 6·8. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%), and 3,9-dioxa-1,2-benzocyclononene,[7] b. p. 119—120°/9 mm., were prepared and purified as previously described.

Hydroxymethyl Derivatives from the Diethers.—3,4-Dimethoxybenzyl alcohol,[8] b. p. 165—168°/9 mm. (phenylurethane,[9] m. p. 117—118°), and 3,4-methylenedioxybenzyl alcohol,[10] m. p. 52·0—52·5°, were prepared as previously described. 3,4-*Dimethylenedioxybenzyl alcohol*, b. p. 165—167°/8 mm. (Found: C, 65·5; H, 6·1. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%) [*phenylurethane* from ligroin in needles, m. p. 74—74·5° (Found: C, 67·4; H, 5·1; N, 5·2. $C_{16}H_{15}NO_4$ requires C, 67·4; H, 5·3; N, 4·9%)], was obtained in 90% yield by the reduction with lithium aluminium hydride of 3,4-dimethylenedioxybenzaldehyde,[6] m. p. 50—51° [*semicarbazone* from ethanol in plates, m. p. 215—215·5° (Found: C, 54·0; H, 5·0; N, 18·7. $C_{10}H_{11}N_3O_3$ requires C, 54·3; H, 5·0; N, 19·0%)].

3,4-*Trimethylenedioxybenzyl alcohol*, b. p. 146—148°/0·11 mm. (Found: C, 66·9; H, 6·6. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%) [*phenylurethane* from ligroin in needles, m. p. 91—91·5° (Found: C, 68·4; H, 5·5; N, 4·7. $C_{17}H_{17}NO_4$ requires C, 68·2; H, 5·7; N, 4·7%)], was similarly obtained from 3,4-*trimethylenedioxybenzaldehyde*. This compound, b. p. 127—129°/0·25

[2] Brown, "Steric effects in conjugated systems," Ed. Gray, Butterworths, London, 1958, p. 100.
[3] Baddeley, Holt, Smith, and Whittaker, *Nature*, 1951, **168**, 386.
[4] Openshaw, "Laboratory Manual of Organic Analysis," Cambridge, 1948, p. 31.
[5] Perkin, Robinson, and Thomas, *J.*, 1909, **95**, 1979.
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[8] Davidson and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 905.
[9] Tiffeneau, *Bull. Soc. chim. France*, 1911, **9**, 929.
[10] Barger, *J.*, 1908, **93**, 567.

mm. [*semicarbazone* from methanol in needles, m. p. 183—184° (Found: C, 56·4; H, 5·5; N, 17·8. $C_{11}H_{13}N_3O_3$ requires C, 56·2; H, 5·5; N, 17·9%)], was prepared from 3,7-dioxa-1,2-benzocycloheptene by Gattermann's method.[11]

3,4-*Pentamethylenedioxybenzyl alcohol.* 3,9-Dioxa-1,2-benzocyclononene (11 g.) in ethylene chloride (80 ml.) was gradually added to a cold (−7°) solution of acetyl chloride (9·8 g.) and aluminium chloride (8·5 g.) in ethylene chloride (20 ml.). The mixture was poured on ice and hydrochloric acid; the organic layer was separated, washed with water, 2N-sodium hydroxide solution, and again with water, and dried (K_2CO_3). Distillation gave 11-*acetyl*-3,9-*dioxa*-1,2-*benzocyclononene* (10 g.), b. p. 139—140°/0·13 mm. (Found: C, 70·7; H, 7·2. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%) [*semicarbazone* from ethanol in needles, m. p. 198—198·5° (Found: C, 60·2; H, 6·5; N, 15·5. $C_{14}H_{19}N_3O_3$ requires C, 60·6; H, 6·9; N, 15·2%)]. The oxidation of this ketone (16 g.) with alkaline hypochlorite gave 3,9-*dioxa*-1,2-*benzocyclononene*-11-*carboxylic acid* (15·5 g.) which separated from aqueous ethanol in needles, m. p. 138—138·5° (Found: C, 64·6; H, 6·4%; equiv., 223. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%; equiv., 222). The ethyl ester, obtained from the acid (15 g.) by the action of ethanolic hydrogen chloride, was reduced by lithium aluminium hydride (3 g.) and gave the required *benzyl alcohol* (12·2 g.), b. p. 154—156°/0·26 mm. (Found: C, 68·8; H, 7·7. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%) [α-*naphthylurethane* from ligroin in slender needles, m. p. 86·5—87° (Found: N, 3·7. $C_{23}H_{23}NO_4$ requires N, 3·7%)].

Chloromethyl Derivatives from the Diethers.—The following chlorides were prepared from the hydroxymethyl compounds as previously described;[1] 3,4-dimethoxybenzyl chloride,[12] m. p. 50—50·5° (Found: Cl, 18·8. Calc. for $C_9H_{11}O_2Cl$: Cl, 19·0%); 3,4-methylenedioxybenzyl chloride,[13] m. p. 23—23·5° (Found: Cl, 20·1. Calc. for $C_8H_7ClO_2$: Cl, 20·8%); 3,4-*dimethylenedioxybenzyl chloride*, b. p. 124—125°/0·07 mm. (Found: C, 58·3; H, 4·8; Cl, 19·2. $C_9H_9ClO_2$ requires C, 58·5; H, 4·9; Cl, 19·2%); 3,4-*trimethylenedioxybenzyl chloride*, b. p. 128°/0·11 mm. (Found: C, 60·8; H, 5·7; Cl, 17·7. $C_{10}H_{11}ClO_2$ requires C, 60·5; H, 5·5; Cl, 17·9%); and 3,4-*pentamethylenedioxybenzyl chloride*, b. p. 143°/0·35 mm. (Found: C, 63·6; H, 6·8; Cl, 15·3. $C_{12}H_{15}ClO_2$ requires C, 63·6; H, 6·6; Cl, 15·7%).

The rates of bromination of the diethers in acetic acid, the rates of solvolysis of the chloromethyl derivatives in 90% aqueous ethanol, and the ultraviolet absorption spectra of the ethers in hexane were measured by the techniques previously described.[1]

The kinetic data are listed in Tables 1, 2, and 3, and the values of $\lambda_{max.}$ and ε in Table 4.

TABLE 4. *Ultraviolet absorption spectra of the diethers in hexane.*

	$\lambda_{max.}$				ε	
Veratrole	2830	2770	2730	1780	2336	2264
1,3-Dioxaindane	2900	2840	2800	2328	3122	2992
1,4-Dioxatetralin	2840	2780	2750 *	2384	2340	
3,7-Dioxa-1,2-benzocycloheptene	2810 *	2750	2690 *		1360	
3,9-Dioxa-1,2-benzocyclononene	2810 *	2750	2700		1322	1318

* Shoulder.

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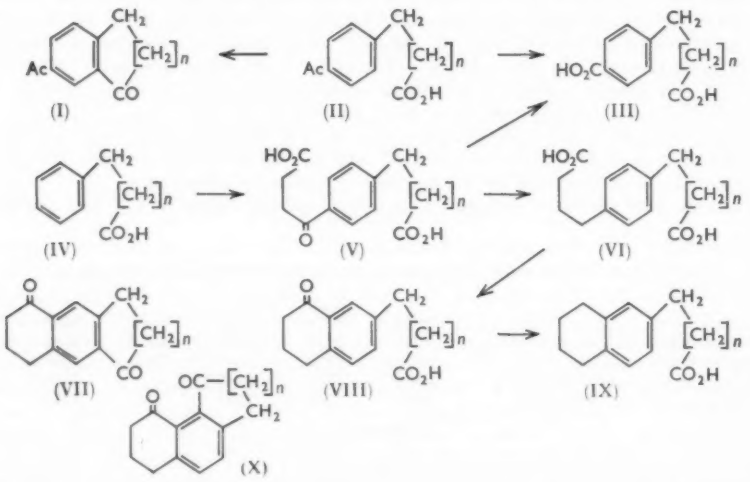
[11] Gattermann, *Ber.*, 1898, **31**, 1150.
[12] Decker and Pschorr, *Ber.*, 1904, **37**, 3404.
[13] Decker and Koch, *Ber.*, 1905, **38**, 1741.

484. *Intramolecular Acylation. An Attempt to Cyclise β-(8-Oxo-2-tetralyl)propionic and γ-(8-Oxo-2-tetralyl)butyric Acids.*

By M. S. Ahmad and G. Baddeley.

The novel keto-acids (VIII; $n = 1$ and 2) have been prepared and heated with an excess of aluminium chloride: the yields of the products of cyclisation, $C_{13}H_{12}O_2$ and $C_{14}H_{14}O_2$, respectively, were only about 5%. We conclude, therefore, that whereas β-4-acylphenylpropionic acid and γ-4-acylphenylbutyric acid are readily cyclised (see II ⟶ I; $n = 1$ and 2), the cyclisation of the analogues having the acyl group in the 3-position of the phenyl group is a very inefficient process of little preparative importance.

With an excess of Friedel–Crafts acylating agent, benzene and its monoalkyl derivatives can be acylated only once; further reaction, when it occurs, involves dehydrogenation of the alkyl group.[1] Diacylation is readily effected (i) when the benzene ring has a strong *op*-directing group, *e.g.*, *p*-ethylphenol can be acylated in both the 2- and the 6-position, and (ii) when the acyl group in the monoacyl derivative is sterically prevented from mesomerically deactivating the benzene ring towards further acylation by having bulky substituents in both *ortho*-positions; thus mesitylene and durene are easily diacylated. These limitations to the Friedel–Crafts acylation of aromatic ketones apply to inter- but not to



intra-molecular acylations, *e.g.*, whereas 1-tetralone cannot be acetylated, γ-*p*-acetylphenylbutyric acid (II; $n = 2$) in the presence of aluminium chloride readily gives 7-acetyl-1-tetralone (I; $n = 2$) by cyclisation.[2] There are numerous examples of intramolecular acylation providing aromatic diketones in which the carbonyl groups are oriented *ortho* to one another (*e.g.*, *o*-benzoylbenzoic acids ⟶ anthraquinones [3]) or *meta* [2] (*e.g.*, see II ⟶ I), but none in which the ring closure occurs in the position *para* to a carbonyl group. We now report an attempt to fill this gap: it involved the preparation of the oxo-acids (VIII; $n = 1$ and 2) and heating them with an excess of aluminium chloride.

Ethyl β-phenylpropionate and γ-phenylbutyrate (IV; $n = 1$ and 2, respectively), in ethylene chloride, dissolved a molecular proportion of aluminium chloride (as $AlCl_3$), and

[1] Baddeley and Wrench, *J.*, 1956, 4943.
[2] Baddeley and Williamson, *J.*, 1956, 4647.
[3] Baddeley, Holt, and Maker, *J.*, 1952, 2415.

when these solutions were added to a mixture of succinic anhydride and aluminium chloride (2 mol.) in ethylene chloride, vigorous reactions occurred at room temperature and gave the half esters of the oxo-dicarboxylic acids (V) in excellent yields. Additional evidence for their structure was obtained by oxidation with dilute nitric acid: the dicarboxylic acids (III) were thereby obtained for comparison with authentic samples. Clemmensen reduction of the compounds (V) and cyclisation of the resulting dicarboxylic acids (VI) with anhydrous hydrofluoric acid gave the novel oxo-acids (VIII; $n = 1$ and 2). Wolff–Kishner reduction of these oxo-acids gave the known acids (IX; $n = 1$ and 2), m. p. 81—82° and 47—49°, respectively.[4] The ring closure (VI ⟶ VIII; $n = 1$) is a further example of the preference for tetralone rather than indanone formation in hydrofluoric acid.

When a molten mixture of the oxo-acid (VIII; $n = 1$) with an excess of aluminium chloride and a little sodium chloride to lower the melting point was heated at 190—200° for 1 hr., subsequent decomposition with ice and hydrochloric acid gave mainly unchanged oxo-acid and an alkali-insoluble tar from which a crystalline compound $C_{13}H_{12}O_2$, m. p. 116—117°, with the properties of an aromatic diketone was isolated. It represents only about 5% of the oxo-acid, and its structure has not been determined. Attempts to improve the yield by heating the reaction mixture at 200° and above for longer than 1 hr. increased only the amount of intractable tar. The oxo-acid (VIII; $n = 2$) behaved similarly and gave a crystalline compound $C_{14}H_{14}O_2$, m. p. 132—133°, in about 5% yield. Apparently, the cyclisation of β-*m*-acylphenylpropionic and γ-*m*-acylphenylbutyric acids differs from that of the isomers having a *p*-acyl group in being a very inefficient process of little if any preparative importance.

Experimental

γ-(p-2-Carboxyethylphenyl)butyric Acid (VI; $n = 1$).—A solution of ethyl β-phenylpropionate (200 g.) and aluminium chloride (152 g.) in ethylene chloride (300 ml.) was gradually added to a cold mixture of succinic anhydride (112 g.) and aluminium chloride (304 g.) in ethylene chloride (600 ml.). A vigorous reaction occurred, and the mixture was kept at room temperature for several hours and was then poured on ice and dilute hydrochloric acid. An emulsion was obtained which was extracted with a large volume of ether. The ether extract was thoroughly washed with sodium hydrogen carbonate solution; acidification of the washings gave β-(*p*-2-ethoxycarbonylethylbenzoyl)propionic acid [5] which separated from dilute ethanol in plates (248 g.), m. p. 113—114° (Found: C, 64·6; H, 6·8. Calc. for $C_{15}H_{18}O_5$: C, 64·7; H, 6·5%). The *semicarbazone* crystallised from ethanol in needles, m. p. 199—200° (Found: C, 57·3; H, 6·6; N, 12·5. $C_{16}H_{21}O_5N_3$ requires C, 57·3; H, 6·3; N, 12·5%). After 8 hr. in a boiling mixture of water (750 ml.) and concentrated nitric acid (50 ml.), the oxodicarboxylic acid (V; $n = 1$) (4·0 g.), obtained by hydrolysis of the above half oxo-ester, gave β-*p*-carboxyphenylpropionic acid, m. p. and mixed m. p. 284—285°; dimethyl ester, m. p. and mixed m. p. 34—35°. After 3 hr. in boiling hydrochloric acid (2N; 2·2 l.), the half oxo-ester (200 g.) gave the oxo-dicarboxylic acid [5] (V; $n = 1$; 144 g.) as plates, m. p. 194—195°, from water (Found: C, 62·7; H, 5·7. Calc. for $C_{13}H_{14}O_5$: C, 62·4; H, 5·6%). This compound was obtained in very poor yield by the interaction of succinic anhydride and β-phenylpropionic acid in the presence of aluminium chloride. Clemmensen reduction of (V; $n = 1$; 140 g.) with amalgamated zinc (300 g.), water (200 ml.), and concentrated hydrochloric acid (700 ml.) required 20 hr. and gave the required *dicarboxylic acid* (VI; $n = 1$; 106 g.) as needles, m. p. 143—144°, from a large volume of water (Found: C, 66·1; H, 6·9. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

p-Bis-3-carboxypropylbenzene (VI; $n = 2$).—A solution of ethyl γ-phenylbutyrate (60 g.) and aluminium chloride (42 g.) in ethylene chloride (100 ml.) was gradually added to a cold (0°) mixture of succinic anhydride (31·3 g.) and aluminium chloride (84 g.) in ethylene chloride (300 ml.); the mixture was then kept at 0° for 15 hr. It was poured on ice and hydrochloric acid, and the organic layer was separated and, together with the ethylene chloride (100 ml.)

[4] Newman and Zahn, *J. Amer. Chem. Soc.*, 1943, **65**, 1097; cf. Darzens, *Compt. rend.*, 1935, **201**, 902.

[5] Borsche and Barthenheier, *Annalen*, 1942, **553**, 250.

extract of the aqueous layer, distilled with steam. The residue gave a solid which was extracted with sodium carbonate solution. Acidification of the extract gave γ-*p*-succinylphenylbutyric acid (V; $n = 2$; 73 g.), m. p. 162—163° after recrystallisation from dilute acetic acid (Found: C, 63·4; H, 6·4. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·1%). Cram, Allinger, and Steinberg [6] give m. p. 164·5°. Oxidation of this compound with dilute nitric acid gave γ-*p*-carboxyphenylbutyric acid, m. p. and mixed m. p. 192—194°. When preparing an authentic sample of this compound by the previously described method,[2] we prepared also the 2,4-*dinitrophenylhydrazone* of ethyl γ-*p*-acetylphenylbutyrate; it separated from ethanol in orange plates, m. p. 136—137° (Found: C, 58·1; H, 5·4; N, 13·2. $C_{20}H_{22}N_4O_6$ requires C, 58·0; H, 5·3; N, 13·5%). Clemmensen reduction of the oxo-dicarboxylic acid (V; $n = 2$; 60 g.) with amalgamated zinc (150 g.), concentrated hydrochloric acid (650 ml.), and water (100 ml.) required 20 hr. and gave *p*-bis-3-carboxypropylbenzene (51 g.) as needles, m. p. 168—171°, from water (Found: C, 66·9; H, 7·4. Calc. for $C_{14}H_{18}O_4$: C, 67·2; H, 7·2%). Cram *et al.*[6] give m. p. 176—177°.

β-(8-*Oxo*-2-*tetralyl*)*propionic Acid* (VIII; $n = 1$).—γ-(*p*-2-Carboxyethylphenyl)butyric acid (VI; $n = 1$; 100 g.) was covered with anhydrous hydrofluoric acid (700 ml.). After several days, the mixture gave a solid residue which was extracted with sodium carbonate solution. The alkaline extract was separated from insoluble material and, when acidified, gave the required *compound* (77·0 g.) which separated from dilute ethanol in rods, m. p. 110—111° (Found: C, 71·2; H, 6·3%; equiv., 216. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·4%; equiv., 218). The *semicarbazone* crystallised from dilute ethanol in plates, m. p. 222—224° (decomp.) (Found: C, 60·7; H, 6·2; N, 15·5. $C_{14}H_{17}O_3N_3$ requires C, 61·1; H, 6·2; N, 15·3%), and the *oxime* in needles, m. p. 201—202° (Found: C, 67·1; H, 6·5; N, 6·1. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·4; N, 6·0%). A mixture of the semicarbazone (1·0 g.) and sodium hydroxide (1·5 g.) in water (3 ml.) and ethylene glycol (30 ml.) was kept at 180—200° for 6 hr. The solvent was then removed under reduced pressure, the residue was dissolved in water, and the solution was acidified. The solid was crystallised from light petroleum and gave β-2-tetralylpropionic acid [4] (0·5 g.) as plates, m. p. 81—82° (Found: C, 76·3; H, 8·0. Calc. for $C_{13}H_{16}O_2$: C, 76·4; H, 7·8%). This acid was obtained in lower yield by Clemmensen reduction of compound (VIII; $n = 1$).

γ-(8-*Oxo*-2-*tetralyl*)*butyric Acid* (VIII; $n = 2$).—This *oxo-acid* (26 g.) was obtained from *p*-bis-3-carboxypropylbenzene (30 g.) by the action of anhydrous hydrofluoric acid; it crystallised from dilute ethanol or dilute acetic acid in flat needles, m. p. 86—87° (Found: C, 72·2; H, 7·1%; equiv., 230. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%; equiv., 232). The *semicarbazone* crystallised from dilute ethanol in small needles, m. p. 208—210° (decomp.) (Found: C, 62·7; H, 6·8; N, 14·5. $C_{15}H_{19}N_3O_3$ requires C, 62·3; H, 6·6; N, 14·5%), and the *oxime* in needles, m. p. 124—125° (Found: C, 67·9; H, 6·9; N, 5·9. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%). The semicarbazone with alkali at 180—200° gave γ-2-tetralylbutyric acid, m. p. 48—49° (Found: C, 76·9; H, 8·3. Calc. for $C_{14}H_{18}O_2$: C, 77·0; H, 8·2%).

γ-(8-*Oxo*-2-*tetralyl*)*butyric Acid* (VIII; $n = 2$) *and Aluminium Chloride*.—An intimate mixture of these reactants (2·0 and 7·0 g., respectively) and sodium chloride (0·5 g.) was heated in an oil bath at 190—200° for 1 hr. When decomposed with ice and hydrochloric acid, it gave a solid which was taken up in benzene or chloroform, washed with water, and then extracted with sodium hydrogen carbonate solution. Acidification of this extract gave the unchanged oxo-acid (VIII; $n = 2$), m. p. and mixed m. p. 85—87°. Removal of the solvent from the organic layer gave a red viscous residue which was extracted repeatedly with boiling light petroleum (b. p. 60—80°). These extracts gave yellow plates (0·15 g.), m. p. 132—133° (Found: C, 78·7; H, 6·3. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). This compound has strong infrared absorption bands at 1687 and 1695 cm.$^{-1}$, indicative of conjugated carbonyl groups, and gave a 2,4-*dinitrophenylhydrazone*, m. p. 218—219° (Found: C, 60·6; H, 4·4; N, 14·5. $C_{20}H_{18}N_4O_5$ requires C, 60·9; H, 4·6; N, 14·2%), and *semicarbazone*, m. p. 234—236° (Found: C, 66·7; H, 6·2; N, 15·7. $C_{15}H_{17}N_3O_2$ requires C, 66·4; H, 6·3; N, 15·5%).

β-(8-*Oxo*-2-*tetralyl*)*propionic Acid* (VIII; $n = 1$) *and Aluminium Chloride*.—The procedure was the same as that above and gave the unchanged propionic acid and pale orange needles (0·15 g.), m. p. 116—117° (Found: C, 78·0; H, 6·0. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%). These have strong infrared absorption bands at 1678 and 1718 cm.$^{-1}$ and gave a 2,4-*dinitrophenylhydrazone*, m. p. 233—234° (Found: C, 59·9; H, 4·1; N, 14·3. $C_{19}H_{16}N_4O_5$ requires

[6] Cram, Allinger, and Steinberg, *J. Amer. Chem. Soc.*, 1954, **76**, 6132.

C, 60·0; H, 4·2; N, 14·7%), and a *disemicarbazone*, m. p. 200—201° (Found: C, 57·3; H, 5·8; N, 26·5. $C_{15}H_{18}N_6O_2$ requires C, 57·3; H, 5·7; N, 26·75%).

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485. *Constituents of* Vitex Agnus Castus *Seeds. Part I. Casticin.**

By I. BELIČ, (MRS.) J. BERGANT-DOLAR, and R. A. MORTON.

"Vitexin," isolated by Malet [1] from *Vitex agnus castus*, has now been obtained pure and shown to differ from a flavone obtained from *Vitex lucens* and also designated vitexin. The name casticin is proposed for the compound from *Vitex agnus castus*.

Casticin has been shown to be a quercetagetin derivative, 5,3′-dihydroxy-3,6,7,4′-tetramethoxyflavone.

FROM *Vitex agnus castus*, long known as a medicinal plant,[2] Malet [1] in 1903 obtained two crystalline substances, vitexin and vitexinine. In our investigation of *Vitex agnus castus* seeds a light petroleum extract deposited a crystalline yellow substance, $C_{19}H_{18}O_8$. Its infrared absorption spectrum indicated the presence of hydroxyl and carbonyl groups and aromatic rings, and the ultraviolet absorption was similar to those of the flavones.[3] Moreover, our substance gave several colour reactions characteristic of flavones.[4]

Our flavone is probably identical with the vitexin obtained by Malet, the crystalline form and colour reactions being the same, though from the melting point and analyses his sample was probably impure. The name vitexin is now being used for the flavone obtained from *Vitex lucens*,[5] so we propose the name casticin for the flavone from *Vitex agnus castus* seeds.

Analytical results (C, H, O, and methoxyl) indicate that casticin is a dihydroxytetramethoxyflavone, and it yields a diacetate and a diethyl ether. Exhaustive methylation with dimethyl sulphate yielded a hexamethyl derivative, which proved to be quercetagetin hexamethyl ether. With hydriodic acid casticin afforded a hexahydroxy-derivative, whose ultraviolet absorption spectrum was essentially that reported by Briggs and Locker [6] for quercetagetin and whose hexa-acetate was identical with authentic hexa-*O*-acetylquercetagetin. Thus casticin is a tetramethyl ether of quercetagetin.

Alkaline hydrolysis of casticin and di-*O*-ethylcasticin gave isovanillic and 3-ethoxy-4-methoxybenzoic acid, respectively, so that casticin contains a free 3′-hydroxyl group. Reduction with magnesium and zinc in acid solution [4] gave a crimson colour which indicated a flavone with a 3-methoxyl group. Since the Wilson [4] test was positive, the second free hydroxyl group is probably in position 5. Nevertheless, casticin, artemetin (5-hydroxy-3,6,7,3′,4′-pentamethoxyflavone),[7] and quercetagetin, gave in Hörhammer and Müller's [8] test a yellow colour but no yellow fluorescence with zirconium oxide dichloride as would be expected from a 5-hydroxyflavone. Partial methylation with

* Presented, in part, at 1st Yugoslav Congress Pure Appl. Chem., Zagreb, June, 1960.

[1] Malet, "Étude botanique et chimique du Vitex Agnus-Castus," Thesis, Montpellier, 1903.
[2] Madaus, "Lehrbuch der biologischen Heilmittel," Leipzig, Georg Thieme Verlag, 1938, p. 441.
[3] Skarzynski, *Biochem. Z.*, 1939, **301**, 150.
[4] Geissmann, "Moderne Methoden der Pflanzenanalyse," ed. Paech and Tracey, Springer-Verlag, Berlin, 1955, Vol. III, p. 467.
[5] Briggs and Cambie, *Tetrahedron*, 1958, **3**, 269.
[6] Briggs and Locker, *J.*, 1951, 3136.
[7] Čekan and Herout, *Coll. Czech. Chem. Comm.*, 1956, **21**, 79.
[8] Hörhammer and Müller, *Arch. Pharm.*, 1954, **287**, 310.

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diazomethane could not be achieved by the method of Marini-Bettolo *et al.*[9] or Flores and Herran,[10] but use of dimethyl sulphate gave a product that was separated by chromatography into unchanged casticin and artemetin. Thus casticin is 5,3′-dihydroxy-3,6,7,4′-tetramethoxyflavone. This has not previously been found in Nature.

Experimental

M. p.s were taken on a Kofler hot stage unless otherwise stated. Ultraviolet absorption spectra were determined for 95% ethanol solutions with a Unicam spectrophotometer, model S.P. 500.

Extraction.—The seeds of *Vitex agnus castus* were collected on the Isle of Lošinj, Yugoslavia, during October. The ground seeds were extracted (Soxhlet) with light petroleum (b. p. 30—50°) for 26 hr. and the deposited yellow substance, amounting to 0·1% of the weight of seeds, was filtered off. It crystallised from benzene–light petroleum as prisms, m. p. 186—187°, $\lambda_{max.}$ 258, 350, and 272 infl. mμ (log ε 4·32, 2·37, and 4·06, respectively), $\lambda_{max.}$ in alkaline solution 276 and 380 mμ (log ε 4·70 and 4·14, respectively), $\lambda_{max.}$ (mull) 2·87, 3·47, 6·02, 6·22, 6·28, 6·42, 6·58, 6·69, 6·94, 7·30, 7·80, 7·89, 8·06, 8·19, 8·59, 8·79, 8·93, 9·12, 10·04, 10·29, 11·52, 12·65, 13·04, and 13·71 μ (Found: C, 60·7; H, 4·9; O, 34·3; OMe, 32·1. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·85; O, 34·2; 4OMe, 33·2%). *Casticin* is insoluble in water and cold light petroleum, slightly soluble in hot light petroleum, and readily soluble in acetone, benzene, ethanol, and chloroform. It gives an olive-green colour with ferric chloride solution and a bright yellow precipitate with lead acetate. Reduction with magnesium and hydrochloric acid or with zinc and hydrochloric acid gave a deep crimson colour. In sodium hydroxide or concentrated sulphuric acid it gave an intense yellow colour. The Wilson reaction with an acetone solution of boric and citric acid was positive. Casticin has R_F 0·26 in formamide–benzene–decalin (mobile phase benzene–decalin, 1 : 1, saturated with formamide), appearing in ultraviolet light as a dark brown spot, that gives an orange-red colour when sprayed with diazotised sulphanilic acid.

Casticin (50 mg.) was treated [11] with acetic anhydride (0·5 ml.) and a drop of 60% perchloric acid at room temperature. The *diacetate* (45 mg.), isolated after ½ hr., crystallised from ethanol and then ethyl acetate as colourless needles, m. p. 178—179° (capillary), $\lambda_{max.}$ 276, 335 mμ (log ε 4·18, 4·26) (Found: C, 60·1; H, 4·7; O, 34·9. $C_{23}H_{22}O_{10}$ requires C, 60·3; H, 4·8; O, 34·9%), giving no colour with ferric chloride solution.

Casticin (500 mg.) was refluxed with anhydrous potassium carbonate (5·5 g.) and diethyl sulphate (2 ml.) in acetone (70 ml.) for 48 hr. Evaporation yielded a residue of *diethyl ether* which crystallised from methanol and then light petroleum as colourless needles (450 mg.), m. p. 115—116°, $\lambda_{max.}$ 240, 330 mμ (log ε 3·15, 3·20) (Found: C, 64·0; H, 6·1; O, 29·7. $C_{23}H_{26}O_{10}$ requires C, 64·2; H, 6·1; O, 29·75%), giving a negative ferric chloride reaction.

Methylation of Casticin.—A solution of casticin (100 mg.) in dry acetone (15 ml.) was heated under reflux with anhydrous potassium carbonate (1 g.) and dimethyl sulphate (0·4 ml.) for 6 hr. Colourless needles, m. p. 141—142° (Found: C, 62·5; H, 5·7. Calc. for $C_{21}H_{22}O_8$: C, 62·7; H, 5·5%), were obtained. The m. p. was not depressed on admixture with authentic hexa-*O*-methylquercetagetin. The ultraviolet spectra [$\lambda_{max.}$ 242, 335 mμ (log ε 4·49, 4·54)] and R_F values (dimethylformamide–decalin and formamide–benzene) of the samples were identical.

Demethylation of Casticin.—Casticin (253 mg.) was heated under reflux for 1 hr. with hydriodic acid (6 ml.; *d* 1·7) and acetic anhydride (15 ml.). The yellow precipitate (164 mg.) formed when the mixture was poured into saturated aqueous sodium dithionite, crystallised from ethanol in yellow needles, m. p. >300° (decomp.). The ultraviolet spectrum [$\lambda_{max.}$ 259, 361, and 272 infl. mμ (log ε 4·23, 4·34, and 4·15 respectively)] was identical with that of quercetagetin.[6] The demethylated product (162 mg.), when acetylated as above, gave the hexa-acetate, prisms (from ethyl acetate), m. p. and mixed m. p. 210—211°. The R_F values (formamide–benzene) of the samples were identical.

Hydrolysis of Casticin.—Casticin (100 mg.) was heated under reflux for 4 hr. under nitrogen with ethanolic 20% potassium hydroxide solution (10 ml.). The solvent was then removed

[9] Marini-Bettolo and Chiavarelli, 16th Internat. Congr. Pure Appl. Chem., Paris, 1957, Résumés II, p. 212.
[10] Flores and Herran, *Tetrahedron*, 1958, **2**, 308.
[11] Cf. Briggs and Locker, *J.*, 1949, 2157.

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under reduced pressure and the residue dissolved in water. The solution was saturated with carbon dioxide and extracted with ether. Material obtained from the dried extract (43 mg). recrystallised from ethanol as yellow needles, m. p. 129—130° (Baker, Nodzu, and Robinson [13] give m. p. 129—130° for 2,6-dihydroxy-ω,4,5-trimethoxyacetophenone). The aqueous solution was acidified with sulphuric acid and extracted with ether. The acid (41 mg.) crystallised from ethanol (charcoal) as needles, m. p. 248° (capillary) (Found: OMe, 18·8. Calc. for $C_8H_8O_4$: 1OMe, 18·5%), undepressed in m. p. on admixture with isovanillic acid,[13] with which it was identical in R_F (propan-2-ol–ammonia) and colours of spots. A depression of the m. p. to 224° was observed on its admixture with vanillic acid.

Hydrolysis of Casticin Diethyl Ether.—The ether (385 mg.) was heated under reflux for 10 hr. with ethanolic 20% potassium hydroxide solution (20 ml.). The acidic fraction (219 mg.) was crystallised successively from aqueous ethanol (charcoal) and benzene, forming colourless needles, m. p. 164° (capillary) (Späth and Bernhauer [14] report 3-ethoxy-4-methoxybenzoic acid, m. p. 165—166°).

Partial Methylation of Casticin.—Casticin (570 mg.) was refluxed with anhydrous potassium carbonate (2·5 g.) and dimethyl sulphate (0·06 ml.) in dry acetone (50 ml.) for 2 hr. The solvent was evaporated under reduced pressure. The residue was chromatographed on a column of cellulose powder (Whatman Standard Grade; 200 g.) and formamide (66 g.). Benzene–light petroleum (b. p. 30—40°) (4 : 1) gave first several fractions showing only one spot on paper chromatograms; these were combined and the solvents were evaporated; the residue crystallised from benzene–light petroleum in yellow needles (235 mg.), m. p. 160—161·5° undepressed on admixture with artemetin, and identical with it in ultraviolet spectrum and R_F values (formamide–benzene and dimethylformamide–decalin).

The authors are indebted to Mr. E. Thommen and Dr. W. Schöniger for the microanalyses and to the Department of Organic Chemistry at the University of Liverpool for the infrared spectrum. Authentic artemetin, hexa-*O*-methylquercetagetin, and hexa-*O*-acetylquercetagetin were generously provided by Dr. Z. Čekan, and hexa-*O*-methylquercetagetin by Mr. J. W. W. Morgan. One author (J. B.-D.) thanks the British Council for a Scholarship.

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[13] Baker, Nodzu, and Robinson, *J.*, 1929, 81.
[13] Perkin and Stoyle, *J.*, 1923, **123**, 3171.
[14] Späth and Bernhauer, *Ber.*, 1925, **58**, 203.

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486. *Periodate Oxidation. Part VI.*[1] *Infrared Spectra of Some Hemialdal Esters.*

By R. D. Guthrie.

Hemialdal diesters (acetates, benzoates, and *p*-phenylazobenzoates) have carbonyl stretching absorptions at frequencies higher than those reported for normal esters. Reasons for this phenomenon are discussed. The high carbonyl stretching frequencies of *gem*-diol diacetates are also discussed.

During work on periodate-oxidised carbohydrate derivatives,[1,2] it was observed that acetates of the hemialdal group [·CH(OH)·O·CH(OH)] had ester carbonyl stretching absorptions in the infrared spectrum at frequencies much higher than those normally reported for acetates of carbohydrates or aliphatic alcohols; a similar effect was noted with benzoates and *p*-phenylazobenzoates. Most of the hemialdal compounds studied were esters of periodate-oxidised methyl 4,6-*O*-alkylidene- or -arylidene-α-D-glucosides (I), with the exception of the diacetate of periodate-oxidised methyl α-L-rhamnoside (II). The results obtained, together with those for other compounds studied for comparison, are

[1] Part V, Colbran, Guthrie, and Parsons, *J.*, 1960, 3532.
[2] Guthrie and Honeyman, *J.*, 1959, 2441.

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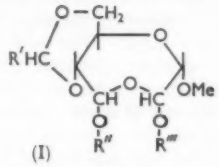
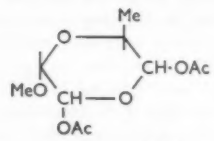
shown in Table 1. Each sample was examined as a mull in Nujol and also as a solution in chloroform; the hemialdal diester values were high in both media. When a spectrum had



(I)



(II)

two carbonyl bonds, both were higher than the normal frequency, showing that vibrational interaction had not occurred. The normal frequencies quoted [3] for saturated esters are 1750—1735 cm.$^{-1}$; for aryl esters, 1730—1717 cm.$^{-1}$.

TABLE 1. *Hemialdal diester frequencies are in bold-face type.*

	$\nu_{C=O}$ (Nujol) (cm.$^{-1}$)	$\nu_{C=O}$ ($CHCl_3$) (cm.$^{-1}$)
Acetates		
1. Ethyl acetate	—	1734
2. 2,3-5,6-Di-*O*-isopropylidene-D-mannose 1-acetate	—	1748
3. 7,9-Diacetoxy-6α-methoxy-2-phenyl-*trans*-*m*-dioxano-[5,4-*e*][1,4]dioxepan,[a] (I; R′ = Ph, R″ = R‴ = Ac) [2]	**1784, 1773**	**1775, 1764**sh
4. 3,5-Diacetoxy-2α-methoxy-6β-methyl-1,4-dioxan (II) [b]	**1770, 1760**sh [c]	**1767**sh, **1757**
5. 7(or 9)-Acetoxy-9(or 7)-benzyloxy-6α-methoxy-2-phenyl-*trans*-*m*-dioxano[5,4-*e*][1,4]dioxepan (I; R′ = Ph, R″ or R‴ = Ph·CH_2, R‴ or R″ = Ac) [2]	1757	—
6. Methyl 4,6-*O*-benzylidene-α-D-glucoside 2,3-diacetate [d]	—	1743
p-*Phenylazobenzoates*		
7. Ethyl *p*-phenylazobenzoate	1719 1713sh	1716
8. 2,3-5,6-Di-*O*-isopropylidene-D-mannose 1-*p*-phenylazobenzoate [e]	1725	1732
9. 2,3,4,6-Tetra-*O*-methyl-D-glucose 1-*p*-phenylazobenzoate [f]	1739	—
10. 6α-Methoxy-2-phenyl-7,9-di-*p*-phenylazobenzoyloxy-*trans*-*m*-dioxano[5,4-*e*][1,4]dioxepan (I, R′ = Ph, R″ = R‴ = Az [g])	**1764, 1751**	**1746**
11. 6α-Methoxy-2-methyl-7,9-di-*p*-phenylazobenzoyloxy-*trans*-*m*-dioxano[5,4-*e*][1,4]dioxepan (I, R′ = Me, R″ = R‴ = Az)	**1762, 1750**	**1747**
Benzoates		
12. Ethyl benzoate	—	1716
13. Methyl 4,6-*O*-benzylidene-α-D-glucoside 2,3-dibenzoate	1726	1731
14. Methyl 4,6-*O*-*o*-bromobenzylidene-α-D-glucoside 2,3-dibenzoate [1]	1725	1729
15. 2,3-5,6-Di-*O*-isopropylidene-D-mannose 1-benzoate [h]	1727	1732
16. 7,9-Dibenzoyloxy-6α-methoxy-2-phenyl-*trans*-*m*-dioxano[5,4-*e*][1,4]dioxepan (I; R′ = Ph, R″ = R‴ = Bz) [2]	**1734**	**1748**
17. 7 9-Dibenzoyloxy-2-*o*-chlorophenyl-6α-methoxy-*trans*-*m*-dioxano[5,4,*e*][1,4]dioxepan (I; R′ = *o*-Cl·C_6H_4, R″ = R‴ = Bz) [1]	**1758, 1746**	**1747**
18. 7(or 9)-Benzoyloxy-2-*o*-chlorophenyl-6α,9(or 7)dimethoxy-*trans*-*m*-dioxano[5,4-*e*][1,4]dioxepan (I; R′ = *o*-Cl·C_6H_4, R″ or R‴ = Bz, R‴ or R″ = Me) [1]	1746	—

sh = shoulder; [a] see ref. 2 for an explanation of this nomenclature; [b] the methyl group is arbitrarily defined as β, so that the original anomeric carbon atom (now C_2) bears the same Greek suffix as in the unoxidised compound); [c] syrup; [d] Bourne, Stacey, Tatlow, and Tatlow, *J.*, 1951, 833; [e] Coleman and McCloskey, *J. Amer. Chem. Soc.*, 1943, **65**, 1588; [f] Freudenberg and Plankenhorn, *Ber.*, 1940, **73**, 621; [g] Az = *p*-C_6H_5·N:N·C_6H_4·CO; [h] Guthrie and Honeyman, *J.*, 1959, 853.

The most marked shift was with the hemialdal acetates (nos. 3 and 4). The *p*-phenylazobenzoates (nos. 10 and 11) showed a more marked change in the solid state than in

[3] Bellamy, "Infrared Spectra of Complex Molecules," Methuen, 1958, p. 178.

solution. The benzoates (nos. 16 and 17) showed a marked shift in solution, but one compound (16) showed a much smaller shift in the solid. The frequency shifts for the spectra of solutions, measured relative to the corresponding ethyl ester, were 30—41 cm.$^{-1}$. In the hemialdal monoesters (nos. 9 and 18; examined in the solid state only), the frequencies were higher than expected, but not as high as for the diesters.

The origin of the large shift is not clear. A field effect [4] would not seem to be the explanation, even though the conformation of the seven-membered ring (in nos. 3, 10, 11, 16, and 17) is not known, since the effect in a six-membered ring was similar (cf. nos. 3 and 4). It is not unreasonable to suppose that in the last compound the acetate groups are equatorial (cf. ref. 5), and hence would not be close to each other. If a field effect were the cause then a similar effect would be expected with sugar αγ- and αβ-diesters, particularly in the latter where the ester groups were axial-equatorial or diequatorial, so that they were close to each other. However, the spectra of methyl 4,6-*O*-benzylidene-α-D-glucoside 2,3-diacetate, methyl 4,6-*O*-benzylidene-, and 4,6-*O*-*o*-bromobenzylidene-α-D-glucoside 2,3-dibenzoates (nos. 6, 13, and 14) had ester carbonyl absorption at lower frequencies than the hemialdal diesters, in chloroform solution.

Another possible explanation is that the inductive effect of the oxygen atom adjacent to the carbon atom bearing the ester group causes the frequency shift (cf. the higher carbonyl frequency in esters that in ketones [6]). To examine this effect some glycosyl esters (nos. 2, 8, 9, and 15) were prepared. The values of the carbonyl stretching frequencies obtained showed a shift of 14—16 cm.$^{-1}$ from the corresponding value for ethyl esters; the shift suggests a slight inductive effect of the oxygen atom. The slightly higher-than-normal value for the hemialdal monoesters (nos. 5 and 18) is probably due to this effect. However, in the hemialdal diesters the inductive effect of the oxygen atom would be shared between the two ester groups and hence should be smaller per ester group; on this reasoning alone the frequency shift should be smaller for hemialdal diesters than for monoesters, and not the reverse as found in practice. Field and inductive effects are shown therefore to be inadequate explanations of this phenomenon.

In searching the literature for analogous phenomena, it was found that 1,1-diacetoxypropane showed [7] an abnormally high ester carbonyl stretching frequency at 1761 cm.$^{-1}$. The spectra of two further examples of *gem*-diol diacetates have now been studied; the carbonyl stretching frequencies, of the same order as that above, are shown in Table 2. This phenomenon was originally attributed to an inductive effect,[7] but has more recently been ascribed to a field effect.[8] The latter would seem more likely as the inductive effect of one acetate group on the other would mutually cancel. It was expected that the frequency of the *o*-phthalaldehyde derivative would be higher than that of benzylidene

TABLE 2. *Carbonyl stretching frequencies of* gem-*diol diacetates.*

	$\nu_{C=O}$ (Nujol) (cm.$^{-1}$)	$\nu_{C=O}$ ($CHCl_3$) (cm.$^{-1}$)
Benzylidene diacetate	1753	1763
Tetra-acetoxy-*o*-phthalaldehyde	1767, 1751	1766br
1,1-Diacetoxypropane [7]	1761 [a]	—

br = broad. [a] Liquid.

diacetate, owing to a greater crowding of the ester groups. No difference was found, except for a broadening of the band.

EXPERIMENTAL

The spectra were examined on a Unicam S.P. 100 infrared spectrometer, fitted with a 1500 lines/in. grating. The compounds were examined as Nujol mulls or as chloroform solutions of 1·5—5·0% concentration. Preparation of new compounds will be described elsewhere.

[4] Ref. 3, p. 400.
[5] Goldstein, Lewis, and Smith, *J. Amer. Chem. Soc.*, 1958, **80**, 939.
[6] Ref. 3, p. 222.
[7] Rasmussen and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1073.
[8] Bellamy and Williams, *J.*, 1957, 861.

The author is indebted to Dr. H. Spedding for helpful discussion and to Miss S. Burgess for experimental assistance. Part of this work was carried out at the University, Leicester; the rest was sponsored by the U.S. Department of Army, through its European Office.

SHIRLEY INSTITUTE, MANCHESTER, 20. [*Received, November 25th*, 1960.]

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487. *Phenylpropiolic Acids. Part VII.* The Self-condensation of 2-Methoxy-4- and -5-methylphenylpropiolic Acid.*

By F. G. BADDAR, E. H. GHALY, and M. F. EL-NEWEIHY.

2-Methoxy-4- and -5-methylphenylpropiolic acid are converted by acetic anhydride into 5-methoxy-7-methyl-1-(2-methoxy-4-methylphenyl)- and 5-methoxy-8-methyl-1-(2-methoxy-5-methylphenyl)-naphthalene-2,3-dicarboxylic anhydride, identical with the cyclisation products from di-(2-methoxy-4- and -5-methylbenzylidene)succinic anhydride, respectively. The first two anhydrides are converted by aluminium chloride into 5,6′-dimethoxy-4′,7- and -3′,8-dimethyl-3,4-benzofluorenone-1-carboxylic acid.

The ultraviolet spectra of the first two anhydrides as well as those of the di(arylmethylene)succinic acids are discussed.

2-METHOXY-4-METHYLPHENYLPROPIOLIC acid was prepared by condensing 2-methoxy-*p*-tolualdehyde with malonic acid in presence of pyridine [1] to give 2-methoxy-4-methylcinnamic acid, which was treated with bromine, then dehydrobrominated to the propiolic acid. When the latter was refluxed with acetic anhydride, it was converted into 5-methoxy-7-methyl-1-(2-methoxy-4-methylphenyl)naphthalene-2,3-dicarboxylic anhydride (IIa). Its structure was established as follows: (i) It is insoluble in sodium carbonate solution, and its cold alkaline solution does not discharge the colour of potassium permanganate; this proved that it is the anhydride of an *ortho*-dibasic acid, and is not a cyclobutadiene derivative.[2] (ii) It is identical with the anhydride obtained by cyclising the anhydride of di-(2-methoxy-4-methylbenzylidene)succinic acid (IIIa) in sunlight.[3] The acid (IIIa) was prepared by condensing 2-methoxy-*p*-tolualdehyde with diethyl succinate in presence of potassium t-butoxide. (iii) Its ultraviolet spectrum is identical with that of 5-methoxy-1-*o*-methoxyphenylnaphthalene-2,3-dicarboxylic anhydride.[4]

The anhydride (IIa) was treated with aluminium chloride in nitrobenzene to give 5,6′-dimethoxy-4′,7-dimethyl-3,4-benzofluorenone-1-carboxylic acid, identified as its methyl ester (IVa; R″ = Me). Decarboxylation of the acid with copper bronze in quinoline gave the fluorenone (V).

2-Methoxy-5-methylphenylpropiolic, prepared from 6-methoxy-*m*-tolualdehyde in a similar manner to the 4-methyl isomer, was refluxed with acetic anhydride to give the naphthalenedicarboxylic anhydride (IIb). Its structure was established by conversion, when heated with ammonium carbonate, into the imide (showing that it is an *ortho*-dibasic anhydride [2]), and by methods analogous to (i—iii) above.

Aluminium chloride in nitrobenzene converted the anhydride (IIb) into 5,6′-dimethoxy-3′,8-dimethyl-3,4-benzofluorenone-1-carboxylic acid (IVb; R″ = H).

The self-condensation of the above arylpropiolic acids takes place through intermediate formation of the anhydrides (Ia and b) (cf. Baddar *et al.*[3,5,6]).

The spectra of the 1-arylnaphthalene-2,3-dicarboxylic anhydrides (IIa and b) are

* Part VI, *J.*, 1959, 1027.

[1] Walling and Wolfstern, *J. Amer. Chem. Soc.*, 1947, **69**, 852.
[2] Cf. Baddar, *J.*, 1947, 224.
[3] Baddar, El-Assal, and Doss, *J.*, 1955, 451.
[4] Baddar and Sawiris, *J.*, 1956, 395.
[5] Baddar and El-Assal, *J.*, 1948, 1267.
[6] Baddar and El-Assal, *J.*, 1951, 1844.

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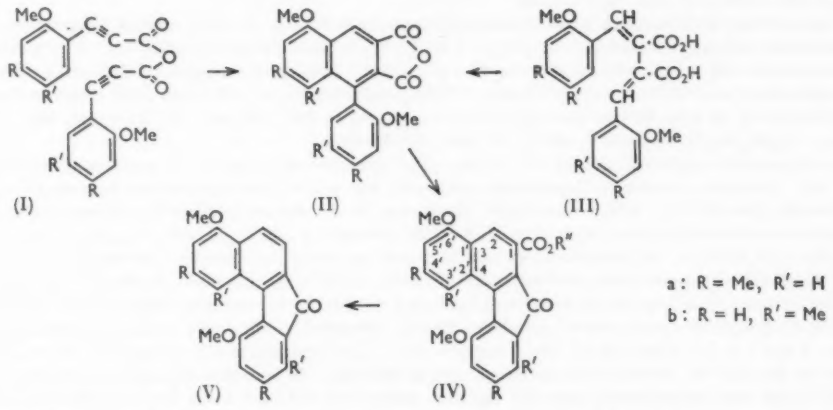
similar to those of 5-methoxy-1-(phenyl- and *o*-methoxyphenyl)naphthalene-2,3-dicarboxylic anhydride.[4] They reveal on comparison with 1-phenylnaphthalene-2,3-dicarboxylic anhydride [4] a bathochromic shift, with a minimum at *ca.* 300 mμ, which is not observed in the parent anhydride. This difference in absorption is reflected in the colour: the new anhydrides are yellow, the parent anhydride is colourless.



The absorption spectra of these molecules are considered to be similar to those of the corresponding naphthalene derivatives.[7]

The hyperchromic effect observed in the absorption of anhydride (IIa) at 274 mμ, when compared with that of (IIb) may be attributed to a slight contribution of the 4′-methyl group in the electronic excitation in the vertical direction, and/or to a slight inhibition of resonance of the phenyl group as a whole with the naphthalene nucleus of (IIb) caused by the 8-methyl group.[4]

The diarylmethylenesuccinic acids (IIIa and b) could be considered as derivatives of 1,4-diphenylbuta-1,3-diene,[8] yet they differ widely from it in their absorption spectra, both in the position of the bands and in their intensity [cf. the spectra of (IIIa and b) (cf. Table) with that of 1,4-diphenylbuta-1,3-diene [8]]. This is probably due to partial inhibition of resonance in the butadiene system by the bulky 2,3-carboxylic groups. The intensity of absorption of acid (IIIa) is higher than that of (IIIb), since in the former compound the methyl group is conjugated with the butadiene system.

Compound	$\lambda_{max.}$ (mμ)	ε	$\lambda_{min.}$ (mμ)	ε
(IIa)	275—274	42,150	302—301	2788
	384—367 †	7966		
(IIb)	274	31,250	304	1580
	~379—376	7782		
	392—380 †	7814		
(IIIa)	283	21,110	311—310	16,240
	332	19,200		
(IIIb)	275—274	18,720	314	10,210
	337	12,270		

~ Inflexion. † Very close bands of poor persistence.

Experimental

Ultraviolet spectra were measured with a Beckman DU spectrophotometer for acetic acid solutions.

2-Methoxy-4- and -5-methylcinnamic Acid.—A mixture of 2-methoxy-*p*-tolualdehyde or

[7] Jones, *Chem. Rev.*, 1943, **32**, 1.
[8] Alberman, Haszeldine, and Kipping, *J.*, 1952, 3284.

6-methoxy-*m*-tolualdehyde (15 g., 1 mol.), malonic acid (15·6 g., 1·5 mol.), ethanol (20 ml.), and pyridine (2·5 ml.) was heated on a boiling-water bath for 7—8 hr., and worked up as usual.[1] *2-Methoxy-4-methylcinnamic acid*, crystallised from ethanol, had m. p. 209° (85%) (Found: C, 68·4; H, 6·3. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). *2-Methoxy-5-methylcinnamic acid*, crystallised from benzene–light petroleum (b. p. 80—100°), had m. p. 147° (47 g., 80%) (Found: C, 68·8; H, 6·4%), and its ethyl ester (prepared by use of hydrogen chloride and ethanol) had b. p. 148—150°/0·5 mm., n_D^{20} 1·5538.

αβ-Dibromo-β-(2-methoxy-4-methylphenyl)propionic Acid.—A boiling stirred suspension of 2-methoxy-4-methylcinnamic acid (10 g., 1 mol.) in carbon tetrachloride (70 ml.) was treated portionwise with a solution of bromine (8·4 g., 1 mol.) in carbon tetrachloride (20 ml.) during 45 min., then stirred for a further 15 min. The product (87%) crystallised from benzene–light petroleum (b. p. 60—80°) to give the *dibromo-acid*, m. p. 155° (Found: C, 37·0; H, 3·3; Br, 45·8. $C_{11}H_{12}Br_2O_3$ requires C, 37·5; H, 3·4; Br, 45·4%).

2-Methoxy-4-methylphenylpropiolic Acid.—The dibromo-acid (50 g., 1 mol.) was refluxed in 20% alcoholic potassium hydroxide (180 ml.) for 6 hr. and worked up as usual.[2] On crystallisation (5·5 g., 21%) from light petroleum (b. p. 60—80°) *2-methoxy-4-methylphenylpropiolic acid* was obtained, with m. p. 155—156° (Found: C, 69·1; H, 5·7. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). An inferior yield was obtained by using the " rapid " method.[9]

Di-(2-methoxy-4-methylbenzylidene)succinic Acid (IIIa).—A mixture of diethyl succinate (5·5 g., 1 mol.) and 2-methoxy-*p*-tolualdehyde (9·5 g., 2 mol.) in dry ether (30 ml.) was quickly added to a stirred suspension of powdered freshly prepared alcohol-free potassium t-butoxide (8 g., 2 mol.) in dry ether (50 ml.) at −15° to −18°. The mixture was kept below 0° for 4 days, then at 20—25° for several hours with occasional stirring. It was decomposed with water, the ether layer was distilled off, and the aqueous layer was refluxed for 2 hr. to hydrolyse any monoethyl ester present. The cold alkaline solution was extracted with ether to remove any neutral material, and the aqueous layer was acidified with hydrochloric acid. The aqueous acidic layer was decanted, the product was extracted 2—3 times with boiling water, and the insoluble acid was filtered off (4·4 g., 36%). It crystallised from acetic acid to give pale yellow *di-(2-methoxy-4-methylbenzylidene)succinic acid*, m. p. 252—253° (Found: C, 68·3; H, 6·1. $C_{22}H_{22}O_6$ requires C, 69·1; H, 5·8%).

5-Methoxy-7-methyl-1-(2-methoxy-4-methylphenyl)naphthalene-2,3-dicarboxylic Anhydride (IIa).—(i) A suspension of di-(2-methoxy-4-methylbenzylidene)succinic acid (0·5 g.) in acetyl chloride (3 ml.) was refluxed for 1 hr. Acetyl chloride was distilled off, and the crude anhydride (*ca.* 0·4 g.), not being easily crystallised, was used directly in the following step.

A solution of di-(2-methoxy-4-methylbenzylidene)succinic anhydride (0·5 g.) in benzene (5 ml.) was treated with a crystal of iodine and left in sunlight for 10 days (March). Distillation of the benzene left a residue which was heated in a vacuum at 100° for 2 hr. Repeated crystallisation from acetic acid gave *5-methoxy-7-methyl-1-(2-methoxy-4-methylphenyl)naphthalene-2,3-dicarboxylic anhydride* in yellow needles, m. p. 238° (Found: C, 72·5; H, 5·2. $C_{22}H_{16}O_5$ requires C, 72·9; H, 5·0%). (ii) 2-Methoxy-4-methylphenylpropiolic acid (5 g.) was refluxed with acetic anhydride (15 ml.) for 3 hr. The product crystallised from acetic acid to give anhydride in yellow needles, m. p. 238° (65—70%), undepressed on admixture with the specimen prepared by method (i).

Methyl 5,6′-Dimethoxy-4′,7-dimethyl-3,4-benzofluorenone-1-carboxylate (IVa; R″ = Me).—Nitrobenzene (18 ml.) was cooled with stirring to −5° and treated portionwise with a finely powdered mixture of the anhydride (1·5 g.) and aluminium chloride (7·5 g.). The whole was kept at 0° for 2—3 hr. and then left at 20—30° for 3 days with occasional stirring. The product was dissolved in aqueous ammonia, and after filtration acidified. The precipitated acid (80%), being difficultly soluble in most organic solvents, was directly esterfied by diazomethane in dioxan–ether. The *methyl ester* crystallised from dioxan in scarlet plates, m. p. 198—199°. Analytical data indicated that the ester contained one molecule of dioxan (Found: C, 70·3; H, 5·7. $C_{23}H_{20}O_5,C_4H_8O_2$ requires C, 69·8; H, 6·1%). Dioxan of crystallisation could only be removed by heating the ester in a vacuum at 150° for *ca.* 24 hr. (Found: C, 72·55; H, 5·4. Calc. for $C_{23}H_{20}O_5$: C, 73·4; H, 5·4%).

5,6′-Dimethoxy-4′,7-dimethyl-3,4-benzofluorenone (V).—The acid (0·2 g.) was stirred in quinoline (7 ml.) at 200—210° for 2—3 hr., during which copper bronze (*ca.* 0·15 g.) was added

[9] Reimer, *J. Amer. Chem. Soc.*, 1942, **64**, 2510.

portionwise. The product crystallised from benzene to give *5,6′-dimethoxy-4′,7-dimethyl-3,4-benzofluorenone* in red plates, m. p. 210—211° (Found: C, 79·4; H, 5·4. $C_{21}H_{18}O_3$ requires C, 79·2; H, 5·7%).

Ethyl α,β-Dibromo-β-(2-methoxy-5-methylphenyl)propionate.—The ice-cold stirred solution of ethyl 2-methoxy-5-methylcinnamate (29 g., 1 mol.) in carbon tetrachloride (60 ml.) was treated portionwise with bromine (25·5 g., 1·2 mol.) in carbon tetrachloride (20 ml.) and stirred for a further hr.,[10] then worked up as usual (yield 85%). On crystallisation from light petroleum (b. p. 60—80°) *ethyl αβ-dibromo-β-(2-methoxy-5-methylphenyl)propionate*, m. p. 127°, was obtained (Found: C, 41·2; H, 4·15; Br, 41·8. $C_{13}H_{16}Br_2O_3$ requires C, 41·1; H, 4·2; Br, 42·05%).

2-Methoxy-5-methylphenylpropiolic Acid.—The above dibromo-ester (10 g., 1 mol.) was treated with 20% alcoholic potassium hydroxide (35 ml.), left for 2 hr. at room temperature, then refluxed for 15 hr. and worked up as usual. The precipitated acid (3·4 g., 68%) crystallised from benzene–light petroleum (b. p. 60—80°) to give *2-methoxy-5-methylphenylpropiolic acid*, m. p. 139° (Found: C, 69·45; H, 5·3. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). The same yield was obtained when the procedure was carried out in two steps.[11]

Di-(2-methoxy-5-methylbenzylidene)succinic Acid (IIIb).—A mixture of diethyl succinate (7·5 g., 1 mol.) and 6-methoxy-*m*-tolualdehyde (13 g., 2 mol.) in dry ether (30 ml.) was quickly added to a stirred suspension of powdered freshly prepared alcohol-free sodium ethoxide (6·8 g., 2 mol.) in dry ether (50 ml.) at −15° to −18°. The reaction was completed as in the analogous experiment, and the precipitated acid (8·3 g., 50%) crystallised from ether–benzene or dilute acetic acid to give *di-(2-methoxy-5-methylbenzylidene)succinic acid* in pale yellow needles, m. p. 207—208° (Found: C, 69·8; H, 5·9. $C_{22}H_{22}O_6$ requires C, 69·1; H, 5·8%).

The *anhydride* was prepared by refluxing the acid (0·5 g.) with acetyl chloride (3 ml.) for 0·5 hr. Removal of the acetyl chloride left a residue, which was triturated with ether, then crystallised from benzene–light petroleum (b. p. 40—60°) in yellow needles, m. p. 230—231° (Found: C, 72·3; H, 5·65. $C_{22}H_{20}O_5$ requires C, 72·5; H, 5·5%).

5-Methoxy-8-methyl-1-(2-methoxy-5-methylphenyl)naphthalene-2,3-dicarboxylic Anhydride (IIb).—(i) A solution of di-(2-methoxy-5-methylbenzylidene)succinic anhydride (0·5 g.) in benzene (10 ml.) and a crystal of iodine were left in sunlight for 12 days (November), and worked up as in the analogous experiment. On crystallisation from acetic acid *5-methoxy-8-methyl-1-(2-methoxy-5-methylphenyl)naphthalene-2,3-dicarboxylic anhydride* was obtained in yellow fine rods, m. p. 243°, depressed to 200—208° on admixture with the original anhydride (Found: C, 72·9; H, 5·05. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%). (ii) 2-Methoxy-5-methylphenylpropiolic acid (5 g.) was refluxed with acetic anhydride (15 ml.) for 3 hr. and worked up as usual. The product (3 g., 64%) crystallised from acetic acid to give the above anhydride in fine yellow rods, m. p. and mixed m. p. 243—244°.

5-Methoxy-8-methyl-1-(2-methoxy-5-methylphenyl)naphthalene-2,3-dicarboximide.—The previous anhydride (1 g.) was thoroughly powdered with ammonium carbonate (1·7 g.), and the mixture heated by a direct flame with frequent shaking until it melted. The mixture was heated gently, being kept just molten, until no more ammonia was evolved. The product, insoluble in sodium carbonate, crystallised from ethanol to give the *imide* in pale yellowish-green crystals, m. p. 278° (0·2 g., 20%) (Found: C, 73·3; H, 5·5; N, 3·9. $C_{22}H_{19}O_4N$ requires C, 73·1; H, 5·3; N, 3·9%). Its infrared spectrum showed a sharp band at 3226 cm.$^{-1}$ (KBr wafer), characteristic of the NH of imides and secondary amides.[12]

5,6′-Dimethoxy-3′,8-dimethyl-3,4-benzofluorenone-1-carboxylic Acid (IVb; R″ = H).—Nitrobenzene (18 ml.) was cooled with stirring to −5°, treated portionwise with a finely powdered mixture of the preceding anhydride (1·5 g.) and aluminium chloride (7·5 g.), and worked up as in the analogous experiment. The precipitated acid (1·2 g., 80%) crystallised from dioxan to give *5,6′-dimethoxy-3′,8-dimethyl-3,4-benzofluorenone-1-carboxylic acid* in needles, m. p. 253—254° (Found: C, 72·4; H, 5·0. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%).

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[10] *Org. Synth.*, Coll. Vol., II, 1943, p. 270.
[11] Hariharan and Sudborough, *J. Indian Inst. Sci.*, 1925, **8**, *A*, 189; *Chem. Abs.*, 1925, **19**, 3263.
[12] Bellamy, " The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., 1956, p. 178.

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488. *Compounds related to the Steroid Hormones. Part II.*[1] *The Action of Hydrogen Bromide on 2-Bromo-3-oxo-Δ¹-5α-Steroids.*

By G. F. H. Green and A. G. Long.

A reaction of the type named in the title, described by Djerassi and Scholz, was believed by them to afford a 4-bromo-Δ¹-3-ketone, from which the corresponding Δ¹,⁴-3-ketone was derived. From 2-bromo-5α-cholest-1-en-3-one (VIII) this reaction has now been traced through the 1,2-dibromides (IV) and (V) to the 1,4-dibromo-ketone (VI); the 1,2-dibromo-compounds can also be derived from 5α-cholest-1-en-3-one (III). Dehydrobromination of the 1,4-dibromo-ketone (VI) gives 4α-bromo-5α-cholest-1-en-3-one (VII) and the 1,4-dien-3-one (IX), which completes a practicable method for making the last-named compound from the Δ¹-3-ketone (III).

Difficulties supervene in the application of these reactions to 4,5α-dihydroprednisone acetate (XII).

Methods of purification, such as differential reactions with the bisulphite ion, are discussed with reference to the preparation of pure specimens of Δ¹- and Δ⁴-3-ketones.

The pharmaceutical value of various steroidal 1,4-dien-3-ones prompted us to study means of making them from 5α-steroids derived commercially from hecogenin. They can be made by dehydrobromination of 2,4-dibromo-3-oxo-5α-steroids, but such bromo-compounds are not always easy to obtain from polyketones, for reasons discussed before.[2] It was accordingly relevant that Djerassi and Scholz [3a] had reported the conversion of an ester of 2-bromo-17β-hydroxyandrost-1-en-3-one into the corresponding 4-bromo-1-en-3-one, by means of hydrogen bromide in acetic acid, and thence by dehydrobromination with collidine into the 1,4-dien-3-one.

We tried their method on 2-bromo-5α-cholest-1-en-3-one (VIII) without success; prolonging the dehydrobromination, however, gave a small yield of cholesta-1,4-dien-3-one (IX). The action of hydrogen bromide in acetic acid on 2-bromo-1-en-3-ones ($\lambda_{max.}$ ~255 mμ) is manifest from the ultraviolet absorption of the products ($\lambda_{max.}$ ~ 234 mμ), but this and the above-mentioned evidence did not rule out the formation also of 1-bromo-Δ¹-3-ones. To test this supposition on a compound unable to rearrange to the 4-bromo-Δ¹-3-ketone, we made 2-bromo-1-dehydroallobetulone (XXII) from allobetulin (XVIII), using a method discussed below with particular reference to 2-bromo-5α-cholest-1-en-3-one (VIII). A solution of the bromoallobetulone (XXII) in acetic acid containing hydrogen bromide suffered little change, which suggests that the formation of 1-bromo-1-en-3-ones is unlikely and that the change in the ultraviolet absorption of compounds that undergo reaction denotes conversion of the 2-bromo-Δ¹-3-oxo- into the 4-bromo-Δ¹-3-oxo-chromophore.

Exploitation of this method needed easier availability of the starting materials: 2-bromo-Δ¹-3-ketones had hitherto been obtained by dehydrobromination of 2,2-dibromo-3-oxo-5α-steroids,[2,4] but this procedure was in some instances tedious and inefficient and was not fully redeemed by improved methods for 2,2-dibromination of 5α-cholestan-3-one (I) and 4,5α-dihydrocortisone acetate (X) in liquid sulphur dioxide (see p. 2537 [5]). A better method for making 2-bromo-Δ¹-3-ketones, described below, is an adaptation of one used by Djerassi and Scholz.[3b]

Acid-catalysed halogenation of simple αβ-unsaturated ketones leads to substitution

[1] Part I, *J.*, 1960, 3333.
[2] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[3] Djerassi and Scholz, *J. Amer. Chem. Soc.*, (*a*) 1947, **69**, 2404; (*b*) 1948, **70**, 1911.
[4] Cf. Inhoffen and Zühlsdorff, *Chem. Ber.*, 1943, **76**, 233; Uskoković, Gut, and Dorfman, *J. Amer. Chem. Soc.*, 1960, **82**, 958.
[5] Ross, Percy, Brandt, Gebhart, Mitchell, and Yolles, *Ind. Eng. Chem.*, 1942, **34**, 924.

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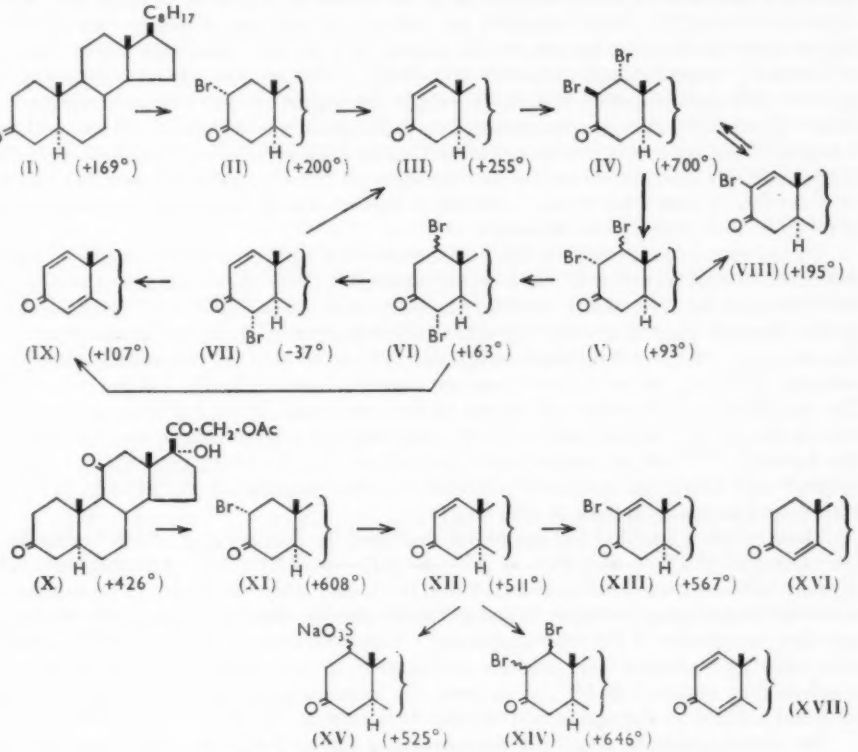
on the α-carbon atom, but in more complicated examples may occur at the α′- and γ-centres.[6] In halogenation of steroidal Δ^1-3-ketones reaction in the γ-position cannot occur, but halogenation of 5α-cholest-1-en-3-one (III) is nevertheless a complex process. We shall now consider this reaction in detail, and show that it controls the rearrangement that leads to the required 4α-bromo-5α-cholest-1-en-3-one (VII).

For reproducible acid-catalysed bromination of the enone (III), certain precautions were needed: for example, addition of a tertiary base immediately after the uptake of halogen considerably improved the yield of one product, 2α-bromo-5α-cholest-1-en-3-one (VIII). The addition of proton acceptors, such as tertiary bases and epoxides has been



Molecular rotations $[M]_D$ are given in parentheses.

advocated in the halogenation of Δ^4-3-ketones to their 4-halogeno-derivatives, the incidence of allylic substitution being curtailed; and Kirk, Patel, and Petrow [7] showed that such acceptors may favour direct substitution as well as influence the changes that follow addition.

When the halogenation of cholest-1-enone (III) in methylene dichloride was not cut short, a sequence of isomerizations and rearrangements ensued, with changes in rotation. We interpret these as follows. Bromine is taken up on the α-face by the 1,2-double bond, and the resulting bromonium ion is cleaved, yielding the *trans*-diaxial 1α,2β-dibromo-compound (IV), which is highly dextrorotatory.[8] In such a *vic*-dibromo-compound a

[6] *E.g.*, Pauly and Berg, *Chem. Ber.*, 1901, **34**, 2092; Hellthaler, *Annalen*, 1914, **406**, 151; Doeuvre, *Bull. Soc. chim. France*, 1926, **39**, 1594.
[7] Kirk, Patel, and Petrow, *J.*, 1956, 627, 1184.
[8] Cf. Fieser and Fieser, "Steroids," Reinhold Publ. Corp., New York, 1959, p. 38.

subsequent change to the diequatorial 1β,2α-form may be expected, or only the 2-bromo-atom may be epimerized;[9] the direction of rotational change would accord with inversion at the 2-position, but this does not allow us to interpret the stereochemistry at $C_{(1)}$. One bromine atom then migrates from the 2- to the 4-position, so that the final product is the 1,4-dibromo-3-ketone (VI), the last rearrangement being accompanied by an increase in dextrorotation. We can now amplify this evidence by considering bromination in acetic acid, during which the products tended to crystallise out; rotational changes were consequently more difficult to record continuously.

Addition of 1 mole of bromine to an acetic acid solution of the steroid (III) was succeeded immediately by crystallization of the dibromide regarded as 1α,2β-dibromo-5α-cholestan-3-one (IV). This dissolved on addition of hydrogen bromide. In mild conditions the 1ξ,2α-dibromo-isomer (V) was formed thereby and could with a little difficulty be isolated; when the concentration of hydrogen bromide was raised, crystals of yet another dibromo-compound separated, which we regard as 1ξ,4α-dibromocholestanone (VI). We lack evidence of spontaneous dehydrobromination in these conditions, although 4-bromo-Δ^1-3-ketones might arise in the methods of isolation used by Djerassi and Scholz.[3a] Dehydrobromination by means of cold pyridine or collidine gave 2-bromo-5α-cholest-1-en-3-one (VIII) from each of the 1,2-dibromo-isomers and 4α-bromo-5α-cholest-1-en-3-one (VII) from the 1,4-dibromo-compound.

The structures suggested for the above-mentioned compounds are upheld by further evidence. Dehalogenation of the 4-bromo-compound (VII) with chromous chloride gave cholest-1-en-3-one (III), which confirms the position of the double bond; the site occupied by the bromine atom is revealed by dehydrobromination to cholesta-1,4-dien-3-one (IX). The structure of the 1,4-dibromo-compound (VI) is verified by dehydrobromination in suitable conditions, either to the foregoing 4-bromo-enone or to the 1,4-dien-3-one (IX). The magnitude of the rotational change in the conversion of the 1,2-dibromo-ketone (V) into its isomer (VI) did not tally with that expected for a simple migration from the 2- to the 4-position,[2,10] but we cannot assess the effects due to the 1-bromo-atom. Spectroscopic[11] and rotational evidence[12] confirms the 4α-configuration in (VI) and (VII) and the 2β- and 2α-configurations in (IV) and (V).

These results show that the conditions described by Djerassi and Scholz[3] bring about the changes (VIII) ⟶ (IV) ⟶ (V) ⟶ (VI) ⟶ (IX). The 1,2-dibromide (IV) is easily derived from 5α-cholest-1-en-3-one (III), and when the latter is brominated in acetic acid containing hydrogen bromide 1,4-dibromo-5α-cholestan-3-one (VI) crystallizes out after completion of the rearrangements. This compound is then dehydrobrominated with dimethylacetamide and calcium carbonate[13] to the required 1,4-dien-3-one (IX), which is thus obtained in 53% yield from the monounsaturated ketone (III); the best we could achieve by the earlier method was 18% from the 2-bromo-ketone (VIII).

The rearrangements described here can also be used for debrominating 2-bromo-Δ^1-3-ketones, for example, conversion of 2-bromo-5α-cholest-1-en-3-one (VIII) successively into the 1,4-dibromo-compound (VI), and the 4-bromo-compound (VII), and 5α-cholest-1-en-3-one (III). We have found zinc and acetic acid or ethanol unsatisfactory for the direct debromination of 2-bromo-Δ^1-ketones.[14]

Application of the new methods to 4,5α-dihydroprednisone acetate (XII) achieved limited success. An improved preparation of the 2-bromo-1-dehydro-compound (XIII)

[9] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175; Corey and Sneen, *ibid.*, 1956, **78**, 6269; cf. Allinger and Allinger, *Tetrahedron*, 1958, **2**, 64; Barton and Cookson, *Quart. Rev.*, 1956, **10**, 70.

[10] Ref. 8, p. 283; Djerassi, *J. Org. Chem.*, 1947, **12**, 823; Djerassi and Sneen, *ibid.*, 1948, **13**, 697; Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4081.

[11] Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.

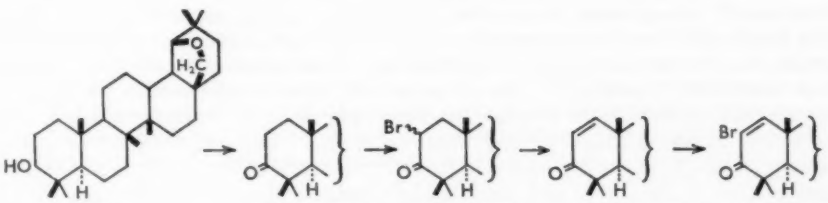
[12] Djerassi, Osiecki, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 1216.

[13] Cf. Joly, Warnant, *et al.*, *Bull. Soc. chim. France*, 1958, **366**, 367; Hohensee and Langbein, *Z. physiol. Chem.*, 1959, **315**, 83.

[14] Djerassi and Rosenkranz, *Experientia*, 1951, **7**, 93; Shaw and Stevenson, *J.*, 1955, 3549; Yanagita and Tahara, *J. Org. Chem.*, 1955, **20**, 959.

resulted, but with hydrogen bromide this yielded an unstable and probably impure 1,2-dibromo-ketone. Carrying the modified method through with crude products failed to give prednisone acetate (XVII), and further work along these lines was abandoned. This failure can probably be attributed to the nature of the rearrangements, in which a stationary concentration of bromine exists and over which control can be achieved only if the required intermediate products are formed preferentially or are sufficiently insoluble to be easily segregated. We have assumed that the situation in the shift of bromine from the 2-position is represented by (XXIII), so that with a polyketone all the active centres can vie for the substituent; the thermodynamically stable products may therefore contain no bromine in ring A. This uncertainty is less for conversions involving rearrangements in 2,2-dibromo-compounds, which are faster than the transformations described here.[2,15] The addition of β-naphthol or chromous chloride intercepts bromine in the rearrangement of 2-bromo-5α-cholest-1-en-3-one (VIII) in the presence of hydrogen bromide, but neither this evidence nor the changes of rotation explain the detailed mechanism. The isomerization giving 1,2α-dibromo-5α-cholestan-3-one (V) may not be catalysed by hydrogen bromide; we find that it is not promoted by radiation of 365 mμ. Kirk and Petrow [16] mention that the chlorination of a Δ^1-3-ketone gives a 1,2-dichloro-ketone, then a 2-chloro-Δ^1-3-ketone, and finally a 1,1,2α-trichloro-3-ketone. Rearrangements in such chloro-compounds are probably precluded for the reasons put forward [15] to explain the greater stability of 2,2-dichloro- than of 2,2-dibromo-3-keto-5α-steroids.

According to patents, 4,5β-dihydroprednisone acetate with 2 mol. of bromine yields the 1,2,2- and the 1,2,4-tribromo-derivative; the latter is converted by sodium iodide into the 4-bromo-3-oxo-Δ^1-5β-steroid, which is dehydrobrominated by lithium chloride in dimethylformamide to the 1,4-dien-3-one.[17] Yields are not cited.



(XVIII) (XIX) (+383°) (XX) (+395°) (XXI) (+373°) (XXII) (+486°)

(XXIII) (III)

Dehydrobromination of 4α-bromo-5α-cholest-1-en-3-one (VII) with dimethylacetamide and calcium carbonate is slow, and similar sluggishness with collidine may explain the difficulties in adapting Djerassi and Scholz's method.[3] Dehydrobromination of 4α-bromo-3-oxo-5α-steroids by such methods is also slow, but not that of 1,4- and 2,4-dibromo-3-ketones. It follows that the main reaction of 1,4-dibromocholestanone (VI) with dimethylacetamide and calcium carbonate by-passes the 4-bromo-compound (VII), and that

[15] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.
[16] Kirk and Petrow, *J.*, 1958, 1334.
[17] *E.g.*, Merck and Co. Inc., B.P. 823,940; U.S.P. 2,837,542, 2,846,856, 2,856,416, 2,870,178, 2,904,564.

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neighbouring groups influence these transformations. Dehydrobromination of bromo-ketones by semicarbazide or dinitrophenylhydrazine was not feasible in making 1,4-dien-3-oxo-steroids, which were only with difficulty generated from their hydrazones by the methods available at the time of this work.[18]

In establishing the structures of our products we found contaminants in several compounds thought previously to be pure. For instance, 5α-cholest-1-en-3-one (III) made by dehydrobromination of the 2α-bromo-ketone with dimethylacetamide and calcium carbonate differs slightly from specimens made by dehydrobromination with semicarbazide [19] or by dehalogenation of the 4-bromo-derivative (VII). The differences are attributed to traces of the Δ^4-isomer arising by cine-elimination, which is promoted by certain bases.[20] The contaminant is probably not removed by the usual methods of purification. Again, in the preparation of 4,5α-dihydroprednisone acetate (XII), acid-catalysed monobromination of 4,5α-dihydrocortisone acetate (X) gives small amounts of the 4-bromo-derivative as well as 2-bromo-4,5α-dihydrocortisone acetate (XI):[21] crystallization removes most of the former from the latter, or the latter may be selectively converted into its water-soluble bisulphite derivative, from which it can be readily regenerated.[22] Dehydrobromination of the 2-bromo-compound (XI) to the 1,2-dehydro-compound (XII) is accompanied by cine-elimination, giving cortisone acetate (XVI), particularly when bases such as collidine or dimethylacetamide are used and even in conditions stated to lessen such complications.[13] Conversely, dehydrobromination of 2,4-dibromo- or 4-bromo-4,5α-dihydrocortisone acetate may contaminate the desired cortisone acetate with its Δ^1-isomer (XII). (Sodium iodide in acetone and subsequent dehalogenation were used for the former,[2] and the bases [13] for the latter.) In their behaviour towards Girard reagents [2,23] such isomers are well-nigh indistinguishable, but they can be separated by selective addition of the HSO_3^- ion to the enone system in the Δ^1-compound.[24] The product is a water-soluble 3-oxo-1-sulphonate (XV), from which the Δ^1-3-ketone (XII) can be recovered by treatment with semicarbazide or with dimethylacetamide and calcium carbonate. 1,4-Dien-3-ones do not react with the bisulphite ion in these conditions; 4,5α-dihydrocortisone acetate (X) gives a water-soluble 3-hydroxy-3-sulphonate that regenerates the ketone when the concentration of the HSO_3^- ion is reduced (for example, by the addition of potassium carbonate). The detergent-like properties of the sulphonates from cholestanone and its derivatives limit their utility in separations.

Combination of the Girard and the bisulphite method permits complete resolution of the components in a mixture of 4,5α-dihydrocortisone acetate, the Δ^1-compound (XII), cortisone acetate (XVI), and prednisone acetate (XVII).

Experimental

Unless otherwise stated, solvents were: chloroform for optical rotation and dispersion (solutions about 1% for the former and 0·1% for the latter); ethanol for ultraviolet absorption spectra; carbon disulphide (cholestane and allobetulin derivatives) and bromoform (pregnane derivatives) for the infrared spectra (of which some have been described elsewhere [25]). M. p.s were measured on a Kofler apparatus. Specific rotations given for rotational changes have been calculated on the assumption that the molecular weight is unchanged. Paper chromatography

[18] Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003; Koechlin, Kritchevsky, and Gallagher, *J. Biol. Chem.*, 1950, **184**, 393; cf. Demaecker and Martin, *Bull. Soc. chim. belges*, 1959, **68**, 365; Taub, Hoffsommer, Slates, Kuo, and Wendler, *J. Amer. Chem. Soc.*, 1960, **82**, 4012.
[19] McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5811.
[20] See Gates and Hughes, *Chem. and Ind.*, 1956, 1506; Rosenfeld, Hellman, and Gallagher, *J. Biol. Chem.*, 1956, **222**, 321; Djerassi and Marshall, *J. Amer. Chem. Soc.*, 1958, **80**, 3986, and references therein; cf. Bergmann and Yaroslavsky, *ibid.*, 1959, **81**, 2772; Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 382.
[21] Mattox and Kendall, *J. Biol. Chem.*, 1950, **185**, 593.
[22] Glaxo Laboratories Ltd., B.P. 837,019.
[23] Glaxo Laboratories Ltd., B.P. 788,307; ref. 2.
[24] Glaxo Laboratories Ltd., B.P. 815,832; cf. Knoevenagel, *Chem. Ber.*, 1904, **37**, 4038.
[25] Cummins and Page, *J.*, 1957, 3847.

was carried out with solvent L, and TSTZ as spray reagent.[24] Compounds were identified with authentic specimens by mixed m. p. determinations and infrared spectroscopy.

Commercial 50—60% pyruvic acid was distilled at 16 mm. with a nitrogen leak until yellow material began to come over. A typical product had the assay: ketone (as pyruvic acid), 24%; acid (as pyruvic acid), 60%; water 48% (all w/v); *d ca.* 1·16. Semicarbazide was most conveniently got from the hydrochloride (50 g.) by cooling to 40° a solution in hot water (50 ml.) and adding phenolphthalein; 40% aqueous sodium hydroxide (*ca.* 46 ml.) was run in until the indicator was just coloured, and the solution was evaporated *in vacuo* to dryness; the residue was leached with refluxing dry ethanol (200 ml.) for 30 min., then filtered rapidly; the filtrate yielded, on cooling, the free base (24·2 g., 72%), m. p. 87—92° (capillary). Evaporation of the mother-liquors and re-extraction yielded another 18% of usable material.

Technical collidine (Hopkin and Williams Ltd.) was distilled at 168—170°/760 mm. through a column of glass balls. Infrared spectra indicated that the product consisted of 2,4,6- and 2,3,6-trimethylpyridine in the ratio of 11 : 9. Calcium carbonate for dehydrobrominations was bought in a suitably fine form as Calofort U from J. and E. Sturge Ltd.

The best conditions for preparative dehydrobrominations were established by prior rate-studies, aliquot parts being assessed at various times by spectroscopy, halogen analysis and, when practicable, paper chromatography.

5α-Cholest-1-en-3-one (III).—(i) 2α-Bromo-5α-cholestan-3-one (II) (10·0 g.), finely powdered semicarbazide base (3·0 g., 1·9 mol.), and acetic acid (250 ml.) were heated for 6 min. at the b. p.,[19] becoming orange. Redistilled pyruvic acid (22 ml.) and water (17 ml.) were added, and the solution was refluxed for 20 min., then cooled and poured into water (2 l.). Extraction with methylene dichloride yielded the ketone (III) as a yellow solid (8·2 g.) that crystallized from methanol (charcoal) as yellow plates (5·7 g., 69%), m. p. 97—100°, $[\alpha]_D^{23}$ +67°, $\lambda_{max.}$ 230 mμ (ε 10,200). The yield was raised to 75% by chromatography on alumina of a hexane solution of the residue from the crystallization.

(ii) 2α-Bromo-5α-cholestan-3-one (II) (5·0 g.) was added portionwise to calcium carbonate (4·0 g.) in boiling dimethylacetamide (50 ml.) during 3 min., and refluxing was continued for 14 min. Some of the solvent was distilled off *in vacuo*; the residue was extracted with ether and washed with hydrochloric acid and water. The ether was dried and evaporated, to yield a white solid (4·1 g.) that crystallized from methanol as needles of the ketone (III) (3·4 g., 82%), m. p. 96—99°. An analytical sample had m. p. 98°, $[\alpha]_D^{20}$ +60°, $[\alpha]_{370}$ −400° (min.), $\lambda_{max.}$ 230 mμ (ε 10,200) (Found: C, 84·5; H, 11·5. Calc. for $C_{27}H_{44}O$: C, 84·3; H, 11·5%).

(iii) 3-Acetoxy-5α-cholest-2-ene (0·856 g.) in dry refluxing carbon tetrachloride (30 ml.) was treated with recrystallized *N*-bromosuccinimide (0·40 g., 1·1 mol.), moisture being excluded. After 2 hours' refluxing the mixture was cooled and filtered, and the filtrate (which fumed; presumably it contained acetyl bromide) and washings were washed with water and dried. Evaporation left a gum, which yielded after chromatography on alumina the solid ketone (III) (0·520 g.). Crystallization from ethanol gave material of m. p. 98—99°, $[\alpha]_D^{20}$ +57°, $\lambda_{max.}$ 230 mμ (ε 10,100). This experiment was carried out by Dr. D. Hathway and Mr. L. Stephenson.

A fourth specimen of the ketone (III) was made by dehalogenation of the 4-bromo-Δ^1-3-ketone (VII) (see below). The specimens were examined for their content of the isomeric cholest-4-en-3-one ($\lambda_{max.}$ 241 mμ) by comparison of the ratios of the optical densities at $\lambda_{max.}$ to those at 241 mμ. For the four samples reported above the respective ratios were 1·40, 1·36, 1·38, and 1·42.

2,2-Dibromo-5α-cholestan-3-one.—5α-Cholestan-3-one (I) (1·0 g.), suspended in commercial liquid sulphur dioxide (100 ml.), was treated with 0·96M-bromine in " AnalaR " carbon tetrachloride (6·6 ml., 2·44 mol.) in 4 min. The solution was left for 11 min. more. It still had a bromine colour. Sodium pyrosulphite (5 g.) was added and the steroid extracted into hexane. Evaporation of the washed and dried hexane solution, and trituration of the residue with methanol, yielded a solid (1·34 g.), m. p. 126—134°. Crystallization gave the 2,2-dibromo-ketone (0·778 g., 55%), m. p. 152—156°, $[\alpha]_D^{20}$ +115°, suitable for most purposes. Recrystallization from hexane gave the pure product (0·582 g., 41%), m. p. 155—157°, $[\alpha]_D^{24}$ +118° (Found: C, 59·6; H, 8·3; Br, 29·6. Calc. for $C_{27}H_{44}Br_2O$: C, 59·6; H, 8·15; Br, 29·4%).

Use of the above procedure produced specimens of the *gem*-dibromo-compound devoid

[24] Brooks, Evans, Green, Hunt, Long, Mooney, and Wyman, *J.*, 1958, 4614.

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of 2α,4α-dibromo-5α-cholestan-3-one; production of this contaminant was difficult to avoid in other methods of acid-catalysed bromination.[3,10]

When the brominated sulphur dioxide solution above was set aside for 6½ hr., crystalline 2α,4α-dibromo-5α-cholestan-3-one was isolated in 27% yield. Halogenation for 6 min. with 1·3 mol. of bromine gave pure 2α-bromo-5α-cholestan-3-one (II) in 28% yield. Liquid sulphur dioxide dissolves steroids, particularly polyoxopregnane derivatives, quite easily. Experiments with 3β-acetoxy-5α-ergostan-11-one and 3β,21-diacetoxy-17α-hydroxy-5α-pregnane-11,20-dione suggest that bromination in this solvent may affect the 9-position, albeit slowly.[27]

2-Bromo-5α-cholest-1-en-3-one (VIII).—A solution of 5α-cholest-1-en-3-one (III) (1·0 g.) in methylene dichloride (25 ml.) and dry ether (2·5 ml.) was stirred during the addition in one lot of 0·99M-bromine in methylene dichloride (2·85 ml., 1·08 mol.). Immediately the bromine colour had disappeared (about 1 min.), pyridine (10 ml.) was added. After 30 min. the solution was extracted with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, then dried and evaporated. The gum yielded small plates (1·05 g., 87%) (from methanol), m. p. 97—101°, $\lambda_{max.}$ 256 mμ (ε 7890). A further crystallisation from ether–methanol yielded birefringent plates of the bromo-ketone, m. p. 102—104°, $[\alpha]_D^{24}$ +38°, $\lambda_{max.}$ 255·5 mμ (ε 8065) (Found: C, 70·1; H, 9·2; Br, 17·6. Calc. for $C_{27}H_{43}BrO$: C, 69·95; H, 9·35; Br, 17·2%) {lit.,[3d] m. p. 91·5—92·5°, $[\alpha]_D$ +37°, $\lambda_{max.}$ 256 mμ (ε *ca.* 8500)}.

Poorer yields were obtained if the addition of pyridine after the bromination was delayed.

Action of Hydrogen Bromide on 2-Bromo-5α-cholest-1-en-3-one (VIII).—The bromo-ketone (VIII) (1·20 g.) was treated in dry acetic acid (53 ml.) with 6N-hydrogen bromide in acetic acid (3·47 ml.; finally 0·36N-hydrogen bromide solution) and set aside for 20 hr. in the dark at room temperature; $[\alpha]_D$ +49° ⟶ +34°. Neutralization with sodium hydrogen carbonate and extraction with ether yielded, after evaporation, a gum (1·19 g.), that was crystallized twice from methanol to give a product (0·27 g.), m. p. 94—114°, $[\alpha]_D^{25}$ +8°, $\lambda_{max.}$ 234 mμ ($E_{1\,cm.}^{1\%}$ 162), $\nu_{max.}$ 1692 cm.$^{-1}$ (Found: Br, 17·0%). A pure specimen of a 4-bromo-Δ^1-3-ketone could not be obtained by crystallization, so the foregoing product (0·100 g.) was heated for 7½ hr. under nitrogen in refluxing collidine (5 ml.). The product isolated in the usual way had to be purified by chromatography on alumina (Grade II); even then the material arose as impure crystals of cholesta-1,4-dien-3-one (IX) (0·016 g., 4%), $\lambda_{max.}$ 244 mμ ($E_{1\,cm.}^{1\%}$ 338), $\nu_{max.}$ 1660, 1628, and 880 cm.$^{-1}$ (Found: Br, 3·65%). Except for the longer period needed for the dehydrobromination these conditions are the same as those described by Djerassi and Scholz [3] for such a reaction. Dehydrobromination with calcium carbonate and dimethylacetamide for 25 min. gave the 1,4-dienone (IX) in 18% yield as prisms (from methanol), m. p. 108—111°, $[\alpha]_D^{22}$ +29°, $\lambda_{max.}$ 245 mμ (ε 15,250); we could not improve on this without resort to modified methods for making the 4-bromo-ketone (VII).

A solution of the 2-bromo-ketone (VIII) (0·100 g.) in dry alcohol-free 0·4N-hydrogen bromide in chloroform (20 ml.) reached a constant $[\alpha]_D$ +42° after 100 min.; the $E_{1\,cm.}^{1\%}$ at 255 mμ had by this time reached a minimum value of 30. From such a solution a gum (0·069 g.), $\lambda_{max.}$ 232 mμ ($E_{1\,cm.}^{1\%}$ 128), was isolated.

1α,2β-Dibromo-5α-cholestan-3-one (IV).—5α-Cholest-1-en-3-one (III) (0·50 g.) was treated in dry " AnalaR " acetic acid (11 ml.) with 0·435M-bromine in acetic acid (2·85 ml., 0·95 mol.) in one lot, with swirling. The bromine was rapidly absorbed and crystals formed. After 1 min. these were filtered off as rapidly as possible on a sintered funnel and were washed at once with sodium hydrogen carbonate solution and water. In this way *1α,2β-dibromo-5α-cholestan-3-one* (IV) (0·423 g., 60%), m. p. 80—110°, $[\alpha]_D^{27}$ +120°, $\nu_{max.}$ 1722 cm.$^{-1}$, was obtained (Found: Br, 28·3. $C_{27}H_{44}Br_2O$ requires Br, 29·4%).

Rapid work was essential, as the crystals redissolved in a few minutes. Sunlight appeared to accelerate solution.

Dehydrobromination of 1α,2β-Dibromo-5α-cholestan-3-one (IV).—The dibromo-compound (0·100 g.) was heated in collidine (5 ml.) on the steam-bath for 1 hr., and then set aside at room temperature for 1½ hr. The product was isolated by extraction with ether; washing with dilute hydrochloric acid removed the collidine. The gum crystallized from ether–methanol to yield 2-bromo-5α-cholest-1-en-3-one (VIII) (0·070 g., 82%), m. p. 102—105°, $\lambda_{max.}$ 256 mμ (ε 8160).

1ξ,2α-Dibromo-5α-cholestan-3-one (V).—Polarimetric studies of the rotation ($[\alpha]_D$ +126° ⟶

[27] Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477.

+33°) of the 1α,2β-isomer (IV) in chloroform containing hydrogen bromide led us to expect formation of the 1,2α-dibromo-ketone (V), especially as subsequent dehydrobromination gave a monobromo-enone, $\lambda_{max.}$ 255 mμ. (There was no evidence of a 4-bromo-1-en-3-oxo-chromophore.) The following procedure was adopted to make a specimen of the 1,2α-dibromo-compound (V). 5α-Cholest-1-en-3-one (III) (1·0 g.) in dry methylene dichloride (25 ml.) and ether (2·5 ml.) was treated with 0·90M-bromine in methylene dichloride (3·05 ml., 1·05 mol.) added in one lot. Immediately after the bromine had been taken up (about 1 min.) the solution was stirred vigorously with saturated sodium hydrogen carbonate solution and then with water, dried, and evaporated. The residual gum (1·398 g.) emitted fumes of hydrogen bromide; it was triturated with hexane to yield a white solid (0·310 g., 22%), m. p. 105—106° (decomp.), $[\alpha]_D$ +17°, $\lambda_{max.}$ 256 mμ ($E^{1\%}_{1\,cm.}$ 23 ⟶ 48 in 15½ hr.), $\nu_{max.}$ 1743 and 738 cm.$^{-1}$ (Found: Br, 27·6. Calc. for $C_{27}H_{44}Br_2O$: Br, 29·4%). This was mainly the 1,2α-dibromo-compound (V). Another attempt at making this compound gave the isomer (IV).

Dehydrobromination of 1ξ,2α-*Dibromo-*5α-*cholestan-*3-*one* (V).—The dibromo-compound (72 mg.) was dissolved in purified pyridine (2 ml.) and set aside for 2 hr. Water was added. 2-Bromo-5α-cholest-1-en-3-one (VIII) (54 mg., 88%) crystallized, having m. p. 100—103°, $[\alpha]_D$ +41°, $\lambda_{max.}$ 255 mμ (ε 7800) (Found: Br, 17·1%).

1ξ,4α-*Dibromo-*5α-*cholestan-*3-*one* (VI).—5α-Cholest-1-en-3-one (III) (2·0 g.) was treated in dry acetic acid (50 ml.) with 0·43M-bromine in acetic acid (12·7 ml., 1·05 mol.) in one lot. The bromine colour dispersed rapidly and a white solid was deposited. Hydrogen bromide in acetic acid (7·4N; 12 ml., 1·2N finally) was added; the solid redissolved and the mixture was set aside for 16 hr. After about 1½ hr. crystallization began. The product was filtered off and washed with sodium hydrogen carbonate solution and with water to yield white crystals (2·0 g., 70%), m. p. 114—119°. Some of this material crystallized from hexane as flat rhombs of the *dibromo-ketone* (VI), m. p. 119—121°, $[\alpha]_D^{25}$ +30°, $\nu_{max.}$ 1735 cm.$^{-1}$ (Found: C, 59·4; H, 7·8; Br, 29·8. $C_{27}H_{44}Br_2O$ requires C, 59·6; H, 8·15; Br, 29·4%).

Alternatively, 2-bromo-5α-cholest-1-en-3-one (VIII) (1·0 g.) in dry acetic acid (35 ml.) was treated with 7·4N-hydrogen bromide in acetic acid (7·0 ml., 1·2N finally) and set aside for 64 hr. The liquor became green and deposited crystals. These were filtered off and washed with sodium hydrogen carbonate solution and with water (767 mg., 65%); they had m. p. 113—116° and were identified with the foregoing dibromo-compound (VI).

Dehydrobromination of 1ξ,4α-*Dibromo-*5α-*cholestan-*3-*one* (VI).—Reaction with calcium carbonate and refluxing dimethylacetamide for 20 min. yielded crystals (from methanol) of cholesta-1,4-dien-3-one (IX), m. p. 106—110°, $[\alpha]_D^{25}$ +29°, $\lambda_{max.}$ 244 mμ (ε 14,900), $\nu_{max.}$ 1664 and 888 cm.$^{-1}$. The yield was 76%. Dehydrobromination with collidine gave the 4-bromo-Δ^1-3-ketone (VII) (see below).

4α-*Bromo-*5α-*cholest-*1-*en-*3-*one* (VII).—1ξ,4α-Dibromo-5α-cholestan-3-one (VI) (0·50 g.) was dissolved in collidine (10 ml.) and set aside for 6½ hr. Collidine hydrobromide began to crystallize after 5 min. The product was isolated by extraction with ether and dilute hydrochloric acid, and crystallized from methanol with a little ether as prisms (343 mg., 81%), m. p. 125—127°. Two further crystallizations yielded birefringent prisms of 4α-*bromo-*5α-*cholest-*1-*en-*3-*one* (VII), m. p. 127·5—128·5°, $[\alpha]_D^{22}$ −8°, $[\alpha]_{370}$ −790° (min.), $\lambda_{max.}$ 232·5 mμ (ε 9360) (Found: C, 69·7; H, 9·2; Br, 16·9. $C_{27}H_{43}BrO$ requires C, 69·95; H, 9·3; Br, 17·2%).

Dehydrobromination of 4α-*Bromo-*5α-*cholest-*1-*en-*3-*one* (VII).—To calcium carbonate (0·50 g.) in refluxing dimethylacetamide (20 ml.) was added with stirring a mixture of the bromo-ketone (VII) (0·50 g.) and calcium carbonate (0·30 g.) in one lot. Refluxing and stirring were continued for 105 min. The cooled mixture was acidified and extracted with ether. The yellow gum (0·392 g.) left on evaporation of the ether yielded cholesta-1,4-dien-3-one (IX) (0·293 g., 71%), m. p. 107—110°, $[\alpha]_D^{24}$ +28°, $\lambda_{max.}$ 245 mμ (ε 14,860).

Debromination of 4α-*Bromo-*5α-*cholest-*1-*en-*3-*one* (VII).—The bromo-ketone (VII) (0·20 g.) was treated in " AnalaR " acetone (25 ml.) with concentrated hydrochloric acid (1 ml.) and 2M-chromous chloride solution (2 ml.) under nitrogen, and set aside for 40 min. The mixture was treated with water and extracted with ether. The gum obtained on evaporation yielded 5α-cholest-1-en-3-one (III) (0·131 g., 79%), m. p. 97—99°, $[\alpha]_D^{25}$ +60°, $\lambda_{max.}$ 228·5 mμ (ε 11,100) (Found: C, 84·0; H, 11·4. Calc. for $C_{27}H_{44}O$: C, 84·3; H, 11·5%). The propertier of specimens of this compound made by different methods, have already been mentioned; the above is probably the purest specimen.

Allobetulone (XIX).—Allobetulin (XVIII) (4·0 g.) was dissolved in purified ethyl methyl

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ketone (see below) (300 ml.) at 60° and stirred during the addition [28] in one lot of 0·33M-potassium dichromate in 4N-sulphuric acid (13·5 ml.), and for 4 min. more. A little sodium pyrosulphite was added to remove excess of oxidant, the solution poured into water (2 l.), and the product (3·97 g.) filtered off and washed thoroughly with water. This material, m. p. 228—230°, $[\alpha]_D^{25}$ +85°, was used without further treatment in the bromination stage. A sample of allobetulone (XIX), recrystallized from acetone, had m. p. 234—236°, $[\alpha]_D^{23}$ +87°, $[\alpha]_{310}$ +830° (max) {lit.,[29] m. p. 230—231°, $[\alpha]_D$ +84·4°; m. p. 235—236°}. (Commercial ethyl methyl ketone reacts with the above oxidising solution: it was boiled with chromium trioxide and distilled before use.)

2ξ-*Bromoallobetulone* (XX).—Allobetulone (XIX) (3·0 g.) was dissolved in dry methylene dichloride (120 ml.) and ether (12 ml.), and mechanically stirred. 0·92M-Bromine in methylene dichloride (7·5 ml., 1·0 mol.) was added dropwise in 7 min., and the stirring continued for 5 min. more. There was no significant induction period. The solution was washed with sodium hydrogen carbonate solution and water, then evaporated. Trituration of the residual gum with methanol yielded 2ξ-*bromoallobetulone* * (XX) (3·21 g., 91%), m. p. 212—222° (Found: Br, 16·3%). A similar specimen from another experiment had m. p. 215—220°, $[\alpha]_D^{22}$ +76°, $[\alpha]_{310}$ +720° (max.) (Found: C, 69·0; H, 9·1; Br, 16·3. $C_{30}H_{47}BrO_2$ requires C, 69·3; H, 9·1; Br, 15·4%). It is possible that isomers with ring A in boat and chair forms are produced in this reaction.[30]

1-*Dehydroallobetulone* (XXI).—2ξ-Bromoallobetulone (XX) (1·85 g.) was added portionwise in 4 min. to a boiling suspension of calcium carbonate (1·6 g.) in dimethylacetamide (70 ml.), and boiling continued for 45 min. more. The suspension was cooled and poured into 2N-hydrochloric acid (200 ml.), and the precipitate filtered off and crystallized from aqueous acetone as needles (1·15 g., 74%), m. p. 238—246°, $[\alpha]_D^{24}$ + 84°. After three recrystallizations the material formed needles of 1-*dehydroallobetulone* * (XXI), m. p. 249—251°, $[\alpha]_D^{23}$ +85°, $[\alpha]_{370}$ −730° (min.), $\lambda_{max.}$ 229 mμ (ε 11,060), $\nu_{max.}$ 1672 and 765 cm.$^{-1}$ (Found: C, 82·3; H, 10·9. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%).

2-*Bromo*-1-*dehydroallobetulone* (XXII).—1-Dehydroallobetulone (XXI) (0·822 g.) was dissolved in dry methylene dichloride (33 ml.) and ether (3·3 ml.) and stirred during the addition in 4 min. of 0·57M-bromine in methylene dichloride (3·45 ml., 1·05 mol.). About 90% of the bromine was absorbed rapidly; a yellow colour persisted after this. After 15 min. (total time) pyridine (3 ml.) was added. When a further 15 min. had elapsed the solution (of constant optical rotation) was washed twice with 2N-hydrochloric acid and then with water until neutral. The methylene chloride was evaporated and the gummy residue triturated with methanol to give 2-*bromo*-1-*dehydroallobetulone* (XXII) (0·935 g., 96%), m. p. 249—252°. A sample crystallized twice from methanol formed white needles, m. p. 254—256°, $[\alpha]_D^{23}$ +94°, $\lambda_{max.}$ 257·5 mμ (ε 8020), $\nu_{max.}$ 1690 cm.$^{-1}$ (Found: C, 69·8; H, 9·1; Br, 15·8. $C_{30}H_{45}BrO_2$ requires C, 69·6; H, 8·8; Br, 15·4%).

Treatment of the 2-bromo-ketone (XXII) (0·20 g.) in dry acetic acid (20 ml.) with 7N-hydrobromic acid in acetic acid (1·2 ml.; 0·4N finally) at room temperature did not change the compound; prolongation to 40 hr. still gave 66% of the 2-bromo-ketone, with minor products with $\nu_{max.}$ 1744 and 1232 cm.$^{-1}$ (probably due to acetate groups).

21-*Acetoxy*-2-*bromo*-17α-*hydroxy*-5α-*pregnane*-3,11,20-*trione* (XI).—4,5α-Dihydrocortisone acetate (X) (50 g.) in dry methylene dichloride (500 ml.) and ether (50 ml.) was treated in 5 min. with 2·14M-bromine in methylene dichloride (61 ml., 1·05 mol.). Towards the end of the addition the product began to crystallize. Ether (1 l.) was added, the mixture cooled to −20°, and the product filtered off and washed with ether; it was dried over sodium hydroxide. The crystals (57·1 g., 88%) had m. p. 191—195°, $[\alpha]_D^{24}$ +115°, $\nu_{max.}$ 1742 and 1230, 1725, and 1705 cm.$^{-1}$ [Found: apparent Br, 26·0 (Carius method). Calc. for $C_{23}H_{31}O_6Br,0{\cdot}5CH_2Cl_2$: apparent Br, 26·8%]. The mother-liquors were washed immediately with sodium hydrogen carbonate solution and with water; the organic phase was dried and evaporated and the residue triturated

* Klinot and Vystrčil (*Chem. and nd.*, 1960, 1360) have recently given further information on these compounds

[28] Cf. Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547; Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175.

[29] Schulze and Pieroh, *Chem. Ber.*, 1922, **55**, 2332; Ruzicka, Brüngger, and Gustus, *Helv. Chim. Acta*, 1932, **15**, 634.

[30] Cf. Barton, Lewis, and McGhie, *J.*, 1957, 2907.

with ethyl acetate. In this way more material (3·5 g.), m. p. 190—192°, was obtained, giving a total yield of 60·6 g. (93%).

This method is an improvement on those published previously.[2,31]

Crystallization of the 2-bromo-compound from methylene dichloride alone gave needles, m. p. 192—202° (Found: Br, 16·7. Calc. for $C_{23}H_{31}BrO_6$: Br, 16·5%), devoid of solvent of crystallization and of the band at 740 cm.$^{-1}$ due to methylene dichloride. Recrystallization from methylene dichloride containing 10% of ether gave the solvate.

The preparation of the ketone (XII) *via* its semicarbazone [$\lambda_{max.}$ 267 mμ (ε 26,000) in dioxan] has been described.[2] Recrystallization from acetone and then again from ethyl acetate gave a specimen, m. p. 256·5—257·5°, $[\alpha]_D^{20}$ +134°, $\lambda_{max.}$ 226 mμ (ε 11,200). A specimen made from second crops of the 2-bromo-compound (XI), again *via* the semicarbazone ($\lambda_{max.}$ 269 mμ, ε 22,200), had m. p. 225—240°, $[\alpha]_D^{20}$ +150°, $\lambda_{max.}$ 229·5 mμ (ε 10,300); it contained cortisone acetate (XVI) derived from the 4-bromo-isomer present in the sample of 2-bromodihydrocortisone acetate (XI). Dehydrobromination of the pure 2-bromo-compound (XI) with dimethylacetamide and calcium carbonate (10 minutes' refluxing) gave the ketone (XII), m. p. 248—252°, $[\alpha]_D^{24}$ +130°, $\lambda_{max.}$ 227 mμ (ε 10,700). The ratios of the optical densities in these three samples at $\lambda_{max.}$ to those at 237 mμ (cortisone acetate, $\lambda_{max.}$ 237 mμ) were 1·39, 1·23, and 1·25 respectively; this confirms that the first contains the least cortisone acetate (XVI).

21-Acetoxy-2-bromo-17α-hydroxy-5α-pregn-1-ene-3,11,20-trione (XIII).—21-Acetoxy-17α-hydroxy-5α-pregn-1-ene-3,11,20-trione (XII) (3·0 g.) was stirred in solution in dry methylene dichloride (90 ml.) and ether (9 ml.) and brominated in 5 min. with 1·92M-bromine in methylene dichloride (3·95 ml., 1·025 mol.); the bromine uptake was rapid until almost all was added. The solution was stirred for 2 min. more and pyridine (3 ml.) was then added; after a further 20 min. the solution was washed with 2N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, then evaporated. The crude solid crystallized from methanol as needles (2·87 g., 80%), m. p. 209—212°. A pure specimen (after two further crystallizations) had m. p. 218—219°, $[\alpha]_D^{29}$ +117°, $\lambda_{max.}$ 255 mμ (ε 7940), $\nu_{max.}$ 1742 and 1230, 1724, 1704, 1688, and 1600 cm.$^{-1}$ (Found: C, 57·5; H, 6·4; Br, 16·5. Calc. for $C_{23}H_{29}BrO_6$: C, 57·4; H, 6·1; Br, 16·6%). A specimen made by dehydrobromination of the 2,2-dibromo-3-ketone [2] had m. p. 200—201° (decomp.), $[\alpha]_D^{20}$ +119°, $\lambda_{max.}$ 255 mμ (ε 7530).

Omission of pyridine in experiments of the above type yielded poor and unreliable results (cf. next paragraph).

21-Acetoxy-1ξ,2ξ-dibromo-17α-hydroxy-5α-pregnane-3,11,20-trione (XIV).—21-Acetoxy-17α-hydroxy-5α-pregn-1-ene-3,11,20-trione (XII) (1·0 g.) in dry methylene dichloride (40 ml.) and ether (4 ml.), cooled in ice, was stirred and treated with a drop of hydrogen bromide in chloroform, and then with 0·98M-bromine in methylene dichloride (2·55 ml., 1 mol.) during 7 min. Stirring was continued for 3 min. more and hexane (100 ml.) was added to precipitate the white *1,2-dibromo-compound* (XIV) (1·1 g., 79%), m. p. 109—111° (decomp., capillary), $[\alpha]_D^{21}$ +116° (ethanol-free $CHCl_3$) ⟶ +87° in 140 min., $\nu_{max.}$ 3600—3400, 1740 and 1226, 1716 and 1705 cm.$^{-1}$ (Found: Br, 27·7. $C_{23}H_{30}O_6Br_2$ requires Br, 28·4%). The ultraviolet absorption was observed at intervals on the solution used for polarimetry with the following results, given in the order time (hr.), $\lambda_{max.}$ (mμ), and $E^{1\%}_{1\,cm.}$: 0, *ca.* 250 mμ, 35; 18, 254, 139; 42, 255, 172; 66, 255, 172. At 18 hr. the pH of an aqueous extriact was 4·5.

Action of Zinc and Acetic Acid on 21-Acetoxy-2-bromo-17α-hydroxy-5α-pregn-1-ene-3,11,20-trione (XIII).—The 2-bromo-Δ^1-compound (XIII) (0·50 g.) in chloroform (10 ml.) and acetic acid (10 ml.) was stirred with acid-washed zinc dust (1·5 g.) for 20 hr. at ⩾35°. The product was isolated by means of methylene dichloride. The gum (0·41 g.) obtained yielded crystals (0·10 g.) from acetone of 4,5α-dihydrocortisone acetate [2] (X), m. p. 220—230°, $[\alpha]_D^{25}$ +106°. The gummy residue from the crystallization had no max. from 220 to 290 mμ (Found: Br, 12·0%). Paper chromatography detected four components, of R_P 0·27, 0·50, 0·77, and 0·87.

Action of Hydrogen Bromide on 21-Acetoxy-2-bromo-17α-hydroxy-5α-pregn-1-ene-3,11,20-trione (XIII).—The 2-bromo-ketone (XIII) (0·75 g.) in dry alcohol-free chloroform (7·5 ml.) and acetic acid (20 ml.) was treated with 5·6N-hydrogen bromide in acetic acid (2·5 ml., *i.e.*, finally 0·47N in hydrogen bromide). The $[\alpha]_D$ +71° changed to +29° in 5·5 hr. and to +48° in 22 hr. A product (0·827 g.) (Found: Br, 28·0%) was extracted after 24 hr. with ethyl acetate. Precipitation from aqueous acetic acid gave a buff solid (0·33 g.), R_P 0·95, $\lambda_{max.}$ 230 mμ ($E^{1\%}_{1\,cm.}$

[31] Oliveto, Gerold, and Hershberg, *J. Amer. Chem. Soc.*, 1952, **74**, 2250.

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137), $\nu_{max.}$ 1744 and 1230, 1725, 1706, 1690, and 1598 cm.$^{-1}$. This material could not be further purified, and a pure product could not be obtained from it by dehydrobromination with collidine.

Bromination and dehydrobromination of the ketone (XII) as described by Djerassi and Scholz [3] and with the modified methods of dehydrobromination described herein gave impure bromine-containing products, R_F 0·0, 0·46, 0·61, 0·71, 0·81, and 0·87. The spot at R_F 0·61 [prednisone acetate (XVII), R_F 0·61] was weak.

Sodium 21-*Acetoxy*-17α-*hydroxy*-3,11,20-*trioxo*-5α-*pregnane* 1ξ-*sulphonate* (XV).—The ketone (XII) (4·02 g.) in refluxing ethanol (100 ml.) and ethyl acetate (20 ml.) was treated with sodium pyrosulphite (0·95 g., 1 mol.) in hot water (25 ml.) under nitrogen. After 5½ hr. an aliquot part no longer smelt of sulphur dioxide when acidified, so the main bulk was concentrated *in vacuo* to small volume, and the precipitate filtered off for study as described below. The aqueous filtrate gave a violet colour with the TSTZ reagent,[26] but no precipitate with neutral barium chloride. It was extracted thrice with ethyl acetate; the last extract gave no colour with the TSTZ reagent. These extracts were combined with the precipitate above, and are discussed below. The aqueous solution was then evaporated *in vacuo* to dryness, toluene being evaporated off finally to remove the last traces of water. The desiccated residue was extracted into refluxing anhydrous ethanol, which was then filtered through kieselguhr and concentrated to small bulk. Crystallization from the cooled solution was promoted by additions of benzene. Small rhombs separated of the sulphonate (XV) (1·99 g., 38%), m. p. 223—226° (decomp., capillary), 208—214° (slight decomp., Kofler), $[\alpha]_D^{22}$ +100° (*c* 1·75 in H_2O), R_F 0·0, $\lambda_{max.}$ (in H_2O) 290 mμ ($E^{1\%}_{1\,cm.}$ 1), $\nu_{max.}$ (in Nujol) 1185 and 1038 cm.$^{-1}$, as well as carbonyl absorption, side chain assay (cortisone acetate as standard [22] and allowance for difference in mol. wt.) 103% (Found: C, 52·5; H, 6·4; S, 6·2. Calc. for $C_{23}H_{31}NaO_9S,H_2O$: C, 52·7; H, 6·3; S, 6·1%).[24]

The precipitate and ethyl acetate extracts yielded after combination and evaporation a residue (0·80 g.) that proved to be a nearly 1 : 1 mixture of cortisone acetate (XVI) and its isomer (XII), $\lambda_{max.}$ 233·5 mμ ($E^{1\%}_{1\,cm.}$ 248), R_F 0·61. This result suggests that the sample of Δ^1-3-ketone (XII) used for this experiment contained about 10% of cortisone acetate, arising by cine-elimination during dehydrobromination of the 2-bromo-ketone (XI) with calcium carbonate in dimethylacetamide.

The sulphonate (as its monohydrate) (0·25 g.) was converted into the ketone (XII) by adding it quickly to refluxing dimethylacetamide (5 ml.) containing calcium carbonate (0·25 g.), under nitrogen; refluxing was continued for 20 min. Separation of the steroid into ethyl acetate, which was washed initially with dilute mineral acid, afforded crystals (0·165 g.). Crystallization from ethyl acetate gave the Δ^1-3-ketone (XII) as fine blades and needles (0·118 g., 62%), m. p. 246—248°, $[\alpha]_D^{21}$ +127°, $\lambda_{max.}$ 227 mμ (ε 11,500), R_F 0·65; there was no evidence of contamination by cortisone acetate (XVI).

The above-described conversion was also achieved as follows. The sulphonate (as the hydrate) (0·139 g.) in water (2 ml.) was heated with M-semicarbazide solution (1 ml.) [from semicarbazide hydrochloride (1·115 g.) and sodium acetate trihydrate (1·361 g.) made up to 10 ml. with water) for 3 hr. on the steam-bath. The precipitated needles were washed with water, and straightway extracted exhaustively with ethyl acetate, chloroform, and 5N-hydrochloric acid; [26] evaporation of the organic phases gave a residue that was treated for 2 hr. at 20° with acetic anhydride (1 ml.) and pyridine (1 ml.). Crystallization of the product from ethyl acetate gave the ketone (XII) (0·031 g., 29%), mainly as needles, m. p. 247—248°, $[\alpha]_D^{20}$ +128°, $\lambda_{max.}$ 227·5 mμ (ε 10,650), R_F 0·64.

Separation of a Mixture by the Use of Pyrosulphite.—The mixture comprised cortisone acetate (XVI) (1·0 g.), its isomer (XII) (0·25 g.), and 4,5α-dihydrocortisone acetate (X) (0·25 g.); it was dissolved in refluxing ethanol (100 ml.) and ethyl acetate (10 ml.), and then treated with sodium pyrosulphite (10 g.) in water (20 ml.). The slurry was refluxed for 15 min.; then a solution of the pyrosulphite (50 g.) in hot water (500 ml.) was added. The mixture was left to cool, finally kept at 0°, and the crystalline precipitate (fraction A) filtered off.

The filtrate was twice extracted with ethyl acetate, evaporation of which gave fraction B. The aqueous phase from the extraction was treated with potassium hydrogen carbonate (60 g.) to adjust the pH to 7; extraction with ethyl acetate until the organic phase was no longer optically active and gave no colour with the TSTZ reagent [26] gave, on evaporation, fraction C.

[22] Mader and Buck, *Analyt. Chem.*, 1952, **24**, 666.

The aqueous phase still gave a violet colour with the TSTZ reagent, and presumably contained the 1-sulphonate from the Δ^1-3-ketone (XII), but it was not further examined. (The TSTZ reagent is not affected by sulphites.)

Fraction A (0·83 g.) recrystallized from ethyl acetate, yielding pure cortisone acetate (XVI) (0·77 g.), $\lambda_{max.}$ 237 mμ (ε 15,300), $[\alpha]_D^{20}$ +181° (in acetone). Fraction B (0·115 g.) consisted of a less pure specimen, $\lambda_{max.}$ 237 mμ (ε 13,600). Fraction C (0·23 g.) crystallized from ethyl acetate, giving almost pure 4,5α-dihydrocortisone acetate (X) (0·21 g.), $[\alpha]_D^{20}$ +113°, $\lambda_{max.}$ 240·5 mμ ($E^{1\%}_{1\,cm.}$ 10).

We thank Professor Barton, F.R.S., for a supply of allobetulin.

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489. *Conformation and Reactivity. Part III.*[1] *Kinetics of the Acid-catalysed Hydrolysis of the Methyl Cyclohexane-mono- and -di-carboxylates and 4-t-Butylcyclohexanecarboxylates.*

By N. B. CHAPMAN, J. SHORTER, and K. J. TOYNE.

The acid-catalysed hydrolysis of methyl cyclohexanecarboxylate (in 1 : 1 and 1 : 3 dioxan–water), of all the dimethyl and methyl hydrogen cyclohexanedicarboxylates (in 1 : 3 dioxan–water), and of methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate (in 1 : 1 dioxan–water), has been studied and the Arrhenius activation energies and non-exponential factors have been determined. The rate coefficients for the first stage of hydrolysis of the diesters were obtained by using Widequist's method.[2] From the results for methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate an equatorial methoxycarbonyl group is shown to react 4·8 times more rapidly than an axial methoxycarbonyl group at 90°. On this basis the results for the other esters are discussed in relation to their possible conformations. The methoxycarbonyl group is more stable in the equatorial than in the axial conformation, but the results for acid-catalysed hydrolysis of the *trans*-1,2-esters are best explained by assuming that the compound is diaxial. Polar effects in acid-catalysed hydrolysis of the esters are small. Some of the results obtained by Cavell, Chapman, and Johnson[3] for the alkaline hydrolysis of the esters are discussed in the light of the results for the acid-catalysed hydrolysis, and an attempt has been made to separate polar effects from steric effects in alkaline hydrolysis.

PREVIOUS papers[1,3] in this series have been concerned with the study of molecular conformation by determination of the kinetics of alkaline hydrolysis in aqueous dioxan of the isomeric dimethyl cyclohexanedicarboxylates, the methyl 4-t-butylcyclohexanecarboxylates, and the acetates of the isomeric methylcyclohexanols and related compounds. Other similar work includes the study of the kinetics of alkaline hydrolysis in aqueous methanol of the dimethyl cyclohexanedicarboxylates[4] and of the acid-catalysed esterification with methanol of cyclohexanedicarboxylic acids.[5]

The interpretation of the results for alkaline hydrolysis of diesters is not easy: the second stage of hydrolysis is subject to very large polar effects because the carboxylate group formed in the first stage of hydrolysis repels the attacking hydroxyl ion. Cavell, Chapman, and Johnson[3] showed that at 30° the *cis*-1,3- and the *trans*-1,4-ester had similar

[1] Part II, Chapman, Parker, and Smith, *J.*, 1960, 3634.
[2] Widequist, *Acta Chem. Scand.*, 1950, **4**, 1216; *Arkiv Kemi*, 1955, **8**, 325, 545.
[3] Cavell, Chapman, and Johnson, *J.*, 1960, 1413.
[4] Smith and Fort, *J. Amer. Chem. Soc.*, 1956, **78**, 4000.
[5] Smith and Byrne, *J. Amer. Chem. Soc.*, 1950, **72**, 4407.

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rates of hydrolysis and conformationally were diequatorial; the *cis*-1,4- and the *trans*-1,3-esters were also similar to each other, being necessarily axial-equatorial. With the *trans*-1,2-esters, they concluded that the diester was predominantly diequatorial but that "the monoester ion had characteristics of both conformations and was assumed to be an equilibrium mixture of diaxial and diequatorial conformations with probably a slightly greater proportion of diaxial." This conclusion concerning the *trans*-1,2-esters differs from Smith's view;[4,5] without a very detailed analysis, he concluded that the *trans*-1,2-diacid, diester, and monoester are diaxial.

The acid-catalysed hydrolysis in aqueous dioxan was therefore studied to shed further light on the conformations and also to study polar effects and steric effects separately as has been made possible, to a large extent, by the work of Taft.[6,7] The basic assumption in this treatment, made by Ingold [8] in a series of papers on constitutional factors controlling ester hydrolysis, is that in acid-catalysed hydrolysis, to a first approximation, steric effects alone determine the relative rate coefficient, while in alkaline hydrolysis polar and steric effects operate. Therefore from a study of the acid-catalysed and alkaline hydrolyses in the same solvents those two factors should be separable.

Experimental

Materials.—The esters were usually prepared and purified as described by Cavell, Chapman, and Johnson.[3] Methyl hydrogen *cis*-1,2- and *cis*-1,3-cyclohexanedicarboxylate, however, were also prepared by hydrogenating the corresponding monomethyl phthalates with a 5% rhodium–alumina catalyst (Baker Platinum Co. Ltd.) at room temperature and atmospheric pressure, until the calculated volume of hydrogen had been absorbed. The purity of methyl cyclohexanecarboxylate, the *cis*- and the *trans*-4-t-butyl esters, and all the diesters was tested by using vapour-phase chromatography with an alkali-washed Celite column with 12% of Apiezon L as stationary phase. In all cases single peaks were obtained with no minor peaks.

Dioxan was purified as described previously [3] and had b. p. 101·5°/760 mm., m. p. 11·8°, n_D^{22} 1·4212. Distilled water was passed through an Elgastat deioniser (Type B. 102); after this treatment it had a specific resistance greater than 4 megohm cm. This very high value indicates the removal of all dissolved carbon dioxide. Aqueous solutions of hydrochloric acid were made by diluting constant-boiling hydrochloric acid with the deionised water. Solutions of hydrochloric acid in 1 : 1 dioxan–water were prepared by mixing 1 vol. of pure dioxan (stored under nitrogen and with oxygen-free nitrogen bubbled through before use) with 1 vol. of ~0·02N-hydrochloric acid, and in 1 : 3 dioxan–water by mixing 1 vol. of pure dioxan and 3 vol. of ~0·013N-hydrochloric acid.* These solutions were always prepared immediately before the kinetic experiment and were not stored for any length of time. The resulting ~0·01N-hydrochloric acid was standardised against ~0·01N-sodium hydroxide (previously standardised against potassium hydrogen phthalate), a pH meter (E.I.L. model 23A) being used for the titrations.

Kinetic Measurements.—The ester was weighed accurately in a graduated flask, and the solution of hydrochloric acid in aqueous dioxan added to give 100 ml. of 0·01M-ester solution. Portions (10 ml.) of the solution were pipetted into Pyrex tubes which were placed in a bath of solid carbon dioxide and acetone. Air in the dead space above the frozen solution was blown out with nitrogen, and the tubes were sealed off and then suspended in the thermostat bath. It was found that, under the conditions used for the acid hydrolysis, dioxan may be decomposed slowly with the formation of acids. Exclusion of light retarded this decomposition to such an extent that it was negligible during an experiment.

At intervals a tube was removed and cooled rapidly in water. The contents of the tube were transferred completely to a 50 ml. beaker, deionised water (10 ml.) being used for washing.

* As in the work of Cavell, Chapman, and Johnson [3] most of the esters were studied in the "1 : 3" solvent. Methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate are insufficiently soluble in this solvent, so these were studied in the "1 : 1" solvent. Methyl cyclohexanecarboxylate was studied in both solvents to provide a link between them.

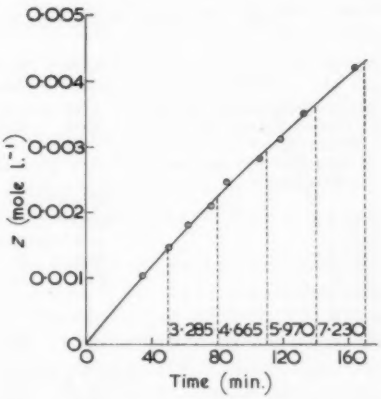
[6] Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 3120.
[7] Taft, *J. Amer. Chem. Soc.*, 1953, **75**, 4231.
[8] Ingold and his co-workers, particularly, *J.*, 1930, 1032.

This solution was titrated with 0·01N-sodium hydroxide by using the pH meter, atmospheric carbon dioxide being excluded with a stream of nitrogen.

By using the first-order rate equation for monoesters $\ln a/(a - x)$ may be plotted against time or, by using the titration volumes, $\ln (T_\infty - T_0)/(T_\infty - T_t)$ against time; the best straight line was drawn through the points. The slope of the line gave the apparent first-order rate coefficient (k_2') for the concentration of hydrochloric acid used in the experiment. To allow for solvent expansion at high temperatures the density of the solvent was determined at several temperatures, and the increase in volume from room temperature to the thermostat temperature calculated. The concentration of hydrochloric acid at room temperature was corrected to give the concentration at the experimental temperature. Division of the apparent first-order rate coefficient by this acid concentration gave the second-order rate coefficient for the acid-catalysed hydrolysis of the monoester (k_2). (Throughout this paper second-order rate coefficients are expressed in l. mole^{-1} sec.$^{-1}$.)

The activation energy, E, and non-exponential factor, A, were determined graphically as usual by using the method of least squares and are accurate to about ± 300 cal. per mole and $\pm 0{\cdot}2$ unit (in log A), respectively.

For the diesters, analysis of the results in terms of the apparent first-order rate coefficients k_1' and k_2' (for the first and the second stage of the hydrolysis respectively) was required.



Plot of z, the concentration of acid produced in hydrolysis, against time. (The area of each of the four strips under the curve is given by the corresponding figure above the abscissa. These give values of A', cf. below and Table 1.)

Frost and Schwemer's method [9] of calculating the rate coefficient for the first of two competitive consecutive second-order reactions, as used, for example, in the alkaline hydrolysis work, cannot be applied to competitive consecutive first-order reactions and so the rate coefficients were calculated by Widequist's method [2] which depends on changing the time variable. The concentration of acid produced by the hydrolysis was plotted against time, and the area under the curve was divided into four strips, with neglect of the initial part of the curve representing the part of the reaction before the tubes had fully reached the thermostat temperature (see Figure). Then the equation derived by Widequist for competitive consecutive first-order reactions was used, *viz.*,

$$k_1' = \frac{z}{2at - A' - (a/k_2')[1 - \exp(-k_2't)]}$$

where k_1' and k_2' are the apparent first-order rate coefficients for the first and the second stage of hydrolysis respectively (k_2' was previously determined from the hydrolysis of the monoester); z is the amount of product per l. formed at time t (measured by the normality of the acid produced in the hydrolysis); a is the initial concentration of diester; and A' is the area under the curve between $t = 0$ and $t = t$, *i.e.*, $A' = \int_0^t z \,.\, dt$.

The equation was adapted for the area under the curve between t_1 and t_2. In this way the

[9] Frost and Schwemer, *J. Amer. Chem. Soc.*, 1952, **74**, 1268.

values of k_1' were determined for four intervals of time and these usually agreed to within 3% (cf. Table 1).

TABLE 1. *Acid-catalysed hydrolysis of dimethyl* trans-1,4-*cyclohexanedicarboxylate at 81·0° in "1 : 3" solvent: an example of the Widequist method.*

$k_2' = 2{\cdot}258 \times 10^{-5}$ sec.$^{-1}$; $a = 0{\cdot}01081$M; Hydrochloric acid = 0·009822N.

t_1 (min.)	t_2 (min.)	$10^6 z_1$ (mole l.$^{-1}$)	$10^6 z_2$ (mole l.$^{-1}$)	A' (mole sec. l.$^{-1}$)	$10^5 k_1'$ (sec.$^{-1}$)
50	80	1435	2220	3·285	4·424
50	110	1435	2975	7·950	4·405
50	140	1435	3680	13·920	4·359
50	170	1435	4360	21·150	4·340

Mean $k_1' = 4{\cdot}38 \times 10^{-5}$ sec.$^{-1}$; $k_1 = 4{\cdot}63 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$ (when corrected for solvent expansion).

The second-order rate coefficient k_1 was then obtained by using the corrected concentration of acid catalyst as before. The Arrhenius parameters, E and log A, were calculated by the method of least squares and are accurate to ±500 cal. per mole and ±0·4 unit respectively. The second-order rate coefficients and Arrhenius parameters for the compounds studied are given in Tables 2 and 3.

TABLE 2. *Rate coefficients (l. mole^{-1} sec.$^{-1}$) for acid-catalysed hydrolysis.*

	Temp. 70·4° 10^4k	81·0° 10^4k	90·3° 10^4k	96·1° 10^4k	100·0° 10^4k	109·4° 10^4k	E (kcal./mole)	log A
Ester								
Me cyclohexanecarboxylate [a]	8·10	15·7	26·2	—	53·0 [d]	74·9	15·0	6·45
Me *trans*-4-Bu^t-cyclohexanecarboxylate [a]	7·94 7·91	15·7	25·1	—	—	74·7	15·0	6·41
Me *cis*-4-Bu^t-cyclohexanecarboxylate [a]	—	4·12 [b]	5·56	7·74	13·1 [f]	16·0	15·3	5·92
Dimethyl cyclohexanedicarboxylates (k_1)								
trans-1,4	23·9	46·3	80·2	—	137	—	15·1	6·97
cis-1,4	15·3	29·2	52·0	—	87·4	—	15·2	6·83
trans-1,3	13·8	26·9	47·3	—	84·2	—	15·6	7·08
cis-1,3	22·3	42·8	75·8	—	132	—	15·4	7·14
trans-1,2	—	—	4·80	7·04	10·4 [e]	17·4 [h]	17·7	7·35
cis-1,2	—	—	4·53	6·61	10·2 [e]	17·3 [g]	18·8	7·97
Me cyclohexanecarboxylate	12·2	25·0	43·2	—	77·0	79·8 76·5	15·6 [c]	7·05
Methyl hydrogen cyclohexanedicarboxylates (k_2)								
trans-1,4	12·4	23·9	42·6	—	75·1 75·1	—	15·6	7·03
cis-1,4 †	8·22	16·2	27·9	—	48·5 48·2	—	15·3	6·63
trans-1,3 †	7·58	15·1	25·7	—	47·4	—	15·7	6·88
cis-1,3 †	12·0	24·3	41·5	—	73·7	—	15·6	7·00
trans-1,2	—	—	2·21	3·28	4·92 [e]	7·93 [h]	17·7	6·99
cis-1,2	—	—	7·46	10·9	16·4 [e]	24·9 [g]	17·0	7·11

[a] In 1 : 1 dioxan–water. All other results refer to 1 : 3 solvent. [b] At 85°. [c] At 100·2°. [d] At 102·2°. [e] At 102·6°. [f] At 105·5°. [g] At 110·0°. [h] At 110·3°.

Values of k are accurate to ±2%, of E to ±300 cal. per mole, and of log A to ±0·2 unit, except for those determined by Widequist's method (see above).

† The alkaline hydrolysis of these monoesters at 25° and 50° was studied to confirm the values obtained by Cavell, Chapman, and Johnson [9] who used the diesters and calculated the rate coefficients by Widequist's [8] and Frost and Schwemer's [9] methods. Mean direct results for "1 : 3" solvent are shown below with the indirect values (10^3k) in parentheses, showing that fair agreement is obtained.

	25°	50°
cis-1,4-Monoester	12·6 (12·3)	48·1 (50·5)
trans-1,3-Monoester	10·8 (9·94)	48·1 (44·3)
cis-1,3-Monoester	37·8 (38·7)	143·5 (148·9)

DISCUSSION

Acid-catalysed Hydrolysis of Methyl Cyclohexanecarboxylate and the Methyl 4-t-Butylcyclohexanecarboxylates.—Winstein and Holness,[10] arguing that a t-butyl group attached

[10] Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

TABLE 3. *Summary of rate coefficients (l. mole^{-1} sec.$^{-1}$) at 90° for acid-catalysed and alkaline hydrolysis in 1 : 3 dioxan–water (calculated from Arrhenius parameters).*

Me_2 cyclohexanedicarboxylates	Acid 10^4k	Alkaline [a] 10^2k	Me hydrogen cyclohexanedicarboxylates	Acid 10^4k	Alkaline [a] 10^2k
trans-1,4	79·1	319	*trans*-1,4	42·2	80·4
cis-1,4-	50·2	151	*cis*-1,4-	27·9	30·1
trans-1,3-	47·1	144	*trans*-1,3-	26·3	25·1
cis-1,3-	74·8	346	*cis*-1,3-	41·8	79·3
trans-1,2-	4·62	51·3	*trans*-1,2-	2·19	2·75
cis-1,2-	4·32	23·8	*cis*-1,2-	7·46	0·587
Me cyclohexanecarboxylate	43·1	67·3			
Me cyclohexanecarboxylate [b]	26·5	37·6			
Me *trans*-4-t-butylcyclohexanecarboxylate [b]	25·8	29·9			
Me *cis*-4-t-butylcyclohexanecarboxylate [b]	5·48	3·60			

[b] In 1 : 1 dioxan–water.
[a] Values obtained from Ref. 3.

to a cyclohexane ring was necessarily in the equatorial conformation, accordingly used the 4-t-butyl group to lock the conformation of substituents at the 1-position in *cis*- and *trans*-isomers, the 1-substituents being respectively axial and equatorial.

From a study of a model of methyl *trans*-4-t-butylcyclohexanecarboxylate, the t-butyl group appears to have no steric effect on the access of a hydrogen ion or a water molecule to the reaction centre, as the t-butyl group is almost entirely hidden from the ester group by the cyclohexane ring. Similarly, in methyl *cis*-4-t-butylcyclohexanecarboxylate the t-butyl group is almost entirely hidden from the ester group by the axial 3- and 5-hydrogen atoms, and no direct steric effect appears possible, although it is conceivable that a small steric effect might be relayed from t-butyl *via* axial hydrogen to the ester group.[11] Further, acid-catalysed hydrolysis is not very sensitive to polar effects,[12] and the t-butyl group in the 4-position is only slightly electron-repelling,[13] so it seems probable that there will be no appreciable polar effect of the 4-t-butyl group in this reaction.

On this basis it follows that the rate coefficients for these two esters give directly the rate coefficients for the axial methoxycarbonyl group as $5{\cdot}48 \times 10^{-4}$ and for the equatorial group as $25{\cdot}8 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ at 90° in 1 : 1 dioxan–water (see Table 3). (All rate coefficients considered in this Section refer to 90°.) The rate coefficient for methyl cyclohexanecarboxylate is $26{\cdot}5 \times 10^{-4}$, *i.e.*, only 3% different from that for methyl *trans*-4-t-butylcyclohexanecarboxylate. This confirms that there is no steric or polar effect of the t-butyl group in methyl *trans*-4-t-butylcyclohexanecarboxylate and suggests also that methyl cyclohexanecarboxylate has its methoxycarbonyl group almost entirely in the equatorial conformation. Similarly, cyclohexyl acetate has its acetoxy-group 92% in the equatorial conformation.[1]

If methyl cyclohexanecarboxylate is assumed to be entirely in the equatorial conformation in " 1 : 3 " solvent, and if the ratio of rate coefficients for equatorial and axial ester group (k_e/k_a) is the same in each solvent, then the rate coefficient for an equatorial ester group in methyl cyclohexanecarboxylate at 90° in " 1 : 3 " solvent is $43{\cdot}1 \times 10^{-4}$ (Table 3) and for an axial ester group is $43{\cdot}1 \times 10^{-4} \times 5{\cdot}48/26{\cdot}1 = 9{\cdot}03 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ ($26{\cdot}1 \times 10^{-4}$ is the average of the values for methyl cyclohexanecarboxylate and methyl *trans*-4-t-butylcyclohexanecarboxylate in 1 : 1 solvent). The ratio of rate coefficients for equatorial and axial groups is therefore ~4·8.

Acid-catalysed Hydrolysis of 1,4- *and* 1,3-*Dimethyl and Methyl Hydrogen Cyclohexanedicarboxylates.*—The *cis*-1,4- and the *trans*-1,3-diester have unambiguous conformations: they must have one group equatorial and one axial. If the ester groups react independently (*i.e.*, neither group exerts a steric or polar effect on the other) then the rate coefficient should be $(9{\cdot}03 + 43{\cdot}1) \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. The observed value is

[11] Cornubert, *Bull. Soc. chim. France*, 1956, 996.
[12] Newman, " Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 587.
[13] Ref. 12, p. 571.

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$50{\cdot}2 \times 10^{-4}$ for the *cis*-1,4-diester and $47{\cdot}1 \times 10^{-4}$ for the *trans*-1,3-diester, agreeing reasonably with the calculated value.

The monoesters, however, may exist with the ester group axial and the carboxyl group equatorial, or *vice versa*. To interpret the results an assumption concerning the properties of the two conformations must be made. The carboxyl and ester groups should differ only slightly in their tendencies to take up axial or equatorial conformations since these tendencies should be governed mainly by interaction of the oxygen atoms with the ring hydrogen atoms, and the presence of OH or OMe should not make much difference. If equilibration takes place after the first stage of hydrolysis to give a monoester with 50% equatorial ester group then the calculated rate coefficient is $(43{\cdot}1 + 9{\cdot}03) \times 10^{-4}/2 = 26{\cdot}1 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. The observed value for the *cis*-1,4-monoester is $27{\cdot}9 \times 10^{-4}$, and for the *trans*-1,3-monoester $26{\cdot}3 \times 10^{-4}$. Any preference would be for the equatorial ester group (unless solvation of the carboxyl group makes it effectively larger than the ester group) which might account for the observed velocity's being slightly higher than that calculated on a 50% basis.

If no equilibration takes place after the first stage of hydrolysis then the monoester will have 17·4% equatorial ester group and 82·6% axial, because in the first stage of hydrolysis the equatorial group is preferentially hydrolysed with respect to the axial group in the ratio of 4·8 : 1. The calculated rate coefficient for a monoester of this composition would be $14{\cdot}9 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. This value is only half the observed value and it is therefore necessary to assume that rapid equilibration takes place.

The *trans*-1,4- and the *cis*-1,3-diester can in principle have both ester groups equatorial or both axial. Inspection of a model suggests that the conformation with both groups equatorial will be that preferred if the interaction of ester group and ring hydrogen is the dominating factor. It being assumed that the esters are entirely in this conformation, then the calculated rate coefficient is $2 \times 43{\cdot}1 \times 10^{-4} = 86{\cdot}2 \times 10^{-4}$, the observed value being $79{\cdot}1 \times 10^{-4}$ for the *trans*-1,4-diester and $74{\cdot}8 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ for the *cis*-1,3-diester. Similarly the *trans*-1,4- and the *cis*-1,3-monoester probably have carboxyl and ester groups both in the equatorial conformation. The calculated rate coefficient is $43{\cdot}1 \times 10^{-4}$, the observed values being $42{\cdot}2 \times 10^{-4}$ and $41{\cdot}8 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, respectively.

It is doubtful whether the deviation of the observed values from those calculated as above is large enough to indicate polar or steric effects in any particular case, especially when the initial assumption is that the ratio of equatorial to axial rate in 1 : 1 dioxan–water is the same as in the 1 : 3 solvent. Another complicating factor is that the *trans*-1,4- and *cis*-1,3-di- and mono-esters may in fact contain a small amount of the diaxial conformation.

It is illogical to suggest a steric effect of the 4-methoxycarbonyl and 4-carboxyl groups when it is assumed that the 4-t-butyl group has no steric effect. Further, inspection of models suggests that steric effects of 3-methoxycarbonyl and 3-carboxyl groups should also be very small. However, the ester and acid groups are fairly powerful electron-attracting groups, and although polar effects in acid hydrolysis are small, such effects may account for differences of the order of 10% between the calculated and the observed rate coefficients. The chlorine atom, which is comparable in size and electron-attracting behaviour[14] to the acid and ester groups, has been shown to have an appreciable polar effect in the acid-catalysed hydrolysis of the straight-chain aliphatic esters,[15] even when separated from the reaction centre by several carbon atoms. For example, the rate coefficient for acid-catalysed hydrolysis in water at 25° for $CH_3{\cdot}[CH_2]_3{\cdot}CO_2Me$ is $7{\cdot}35 \times 10^{-5}$, and for $Cl{\cdot}[CH_2]_3{\cdot}CO_2Me$ is $5{\cdot}19 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$.

In view of the possibility of this polar effect, it may be that the *cis*-1,4- and *trans*-1,3-mono-esters exist with approximately 60% equatorial and 40% axial ester group, rather than with 50% of each. This would give a calculated rate coefficient of

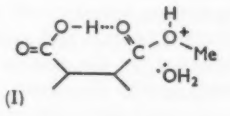
[14] Jaffé, *Chem. Rev.*, 1953, **53**, 191.
[15] Salmi, *Ber.*, 1939, **72**, 1767.

$29{\cdot}4 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, which might be reduced to the observed values of $27{\cdot}9 \times 10^{-4}$ and $26{\cdot}3 \times 10^{-4}$ by polar effects.

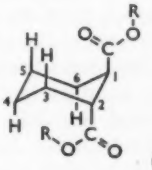
Acid-catalysed Hydrolysis of Dimethyl and Methyl Hydrogen Cyclohexane-1,2-dicarboxylates.—The results for the mono- and di-1,2-esters are more difficult to interpret than those for the 1,3- and 1,4-esters because in the 1,2-esters the groups do not react independently. With the *trans*-1,2-diester the rate coefficient is approximately twice that for the *trans*-1,2-monoester. This 2 : 1 ratio in rate coefficients is not a chance ratio arising from the temperature chosen, since the activation energies are the same within experimental error, and the ratio will therefore be the same over a considerable range of temperature. The ratio is predictable if the two compounds are conformationally similar and it corresponds to a simple statistical factor. The *trans*-1,2-esters can be either diaxial or diequatorial and since the *trans*-1,4- and *cis*-1,3-esters have been shown to exist largely in the diequatorial conformation it is reasonable to assume, in the first place, that the same is true of the *trans*-1,2-esters.[3] The rate coefficient for a diester with two equatorial groups reacting independently is $86{\cdot}1 \times 10^{-4}$ compared with the observed value of $4{\cdot}62 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. Presumably this low value is chiefly due to a primary steric effect, although there will also be a small polar effect.

With the *cis*-1,2-esters the conformation is necessarily axial-equatorial and the distance between the two groups is the same as in the diequatorial conformation of the *trans*-1,2-esters. For the *cis*-1,2-diester the rate coefficient is $4{\cdot}32 \times 10^{-4}$ and the calculated value is $(43{\cdot}1 + 9{\cdot}03) \times 10^{-4} = 52{\cdot}1 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$; the observed value is about 8% of the calculated value, presumably because of a primary steric effect. For the *cis*-1,2-monoester the calculated rate coefficient is $(43{\cdot}1 + 9{\cdot}03) \times 10^{-4}/2 = 26{\cdot}1 \times 10^{-4}$ on the assumption that 50% of the molecules have the ester group equatorial (see interpretation of reactions of *cis*-1,4- and *trans*-1,3-monoesters, p. 2548); the actual value is $7{\cdot}46 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, about 30% of the calculated value. If the *cis*-1,2-monoester had the ester group entirely in the equatorial conformation, then the observed rate coefficient would be 17% of the calculated value. The observed rate coefficient for the monoester is almost twice that for the diester. The reason for this, and for the ratio $k_{obs.}/k_{calc.}$ for the monoester being, even on an extreme assumption about the conformation of the monoester, much higher than that for the diester, may be that the steric effect of the carboxyl group, even when solvated, is less than the steric effect of the methoxycarbonyl group. In the crowded situation the loss of the methyl group in the first stage of hydrolysis might considerably reduce the steric hindrance for the reaction of the second ester group. However, this effect should also operate in the *trans*-1,2-compounds if they were diequatorial, since the distance between the two groups is then the same as in the *cis*-compound, but there is no sign of any such effect.

Another possible explanation for the increase in rate with the *cis*-1,2-monoester compared with the *cis*-1,2-diester is that internal hydrogen-bonding may occur in the monoester, producing a change in electron density at the carbonyl carbon atom of the ester



(I)



(II)

(axial H atoms only are shown)

group, so that the water molecule can attack more easily [see (I)]. This effect may also operate in the *trans*-1,2-monoester if diequatorial, but in this case no such effect is required to account for the results.

It does not therefore seem possible to give an entirely satisfactory explanation of the

rates for all four 1,2-esters on the assumption that the *trans*-1,2-esters are diequatorial, and the other extreme assumption may therefore be considered.[5]

If the *trans*-1,2-esters exist as diaxial compounds then the calculated rate coefficient for the diester is $18{\cdot}1 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, so that the observed value is approximately 25% of the calculated value. However, the two ester groups are so separated that no primary steric effect can occur between the two groups to account for this reduction. It may, however, be accounted for in the following way. An ester group, undergoing acid hydrolysis, will increase in size on attaining the transition state because of the addition of the proton, the attacking water molecule, and other water molecules of solvation. With an isolated axial ester group the increase in size may cause pressure on the 3- and 5-axial hydrogen atoms and consequently buckle the cyclohexane ring to relieve the strain.[16] With another axial ester group (or acid group) present on the other side of the ring, in the 2-position for example, any displacement caused by the ester group undergoing hydrolysis would cause the axial 4- and 6-hydrogen atoms to interact with the ester group (or acid group) in the 2-position [see (II)]. This relayed steric effect may account for the observed reduction in rate.

If the *trans*-1,2-esters are diaxial then the *cis*-1,2-esters are much more crowded than the *trans*-1,2-esters because of the direct ester–ester or ester–acid interactions. If the steric effect of an acid group is less than that of an ester group in the *cis*-1,2-compounds, then this will increase the rate for the monoester as compared with the diester. The reactivity of *cis*-1,2-monoester may also be increased by the hydrogen-bonding effect. Neither of these influences will operate in the *trans*-1,2-monoester if this is diaxial, because the groups will be too far apart.

A peculiar relationship in rate of *cis*-1,2-compounds is also noticeable in the esterification of the *cis*-1,2-di- and mono-acids (monomethyl esters).[5] A preliminary abstract [17] seems to suggest that a similar effect is observed in the acid-catalysed hydrolysis in aqueous acetone. The rates of acid-catalysed hydrolysis of the 1,2-esters in " 1 : 3 " dioxan–water may thus be more satisfactorily explained on the basis of the *trans*-compounds' being diaxial than on the basis of their being diequatorial.

Activation Energies and Non-exponential Factors in Acid-catalysed Hydrolysis.—For the 1,3- and 1,4-positions, compounds with axial ester groups present appear to have a lower non-exponential factor than compounds with equatorial groups. The difference between the values for equatorial and axial ester groups in the same position and with the remaining part of the molecule fixed, is always small but is largest for methyl *trans*- and methyl *cis*-4-t-butylcyclohexanecarboxylate where the ester groups are entirely equatorial and axial respectively. In all other cases, *e.g.*, the *trans*-1,4-diester and *cis*-1,4-diester (and with the monoesters), there is a small difference, with the more axial compounds always having a lower non-exponential factor. This situation is possibly due to " classical steric hindrance " (see discussion of alkaline hydrolysis below). The variation in the value of the activation energy is not regular and is very small, almost covered by the estimated experimental error.

The 1,2-esters are quite different from the 1,3- and 1,4-esters in this respect. The *cis*-1,2-diester has a high activation energy and a high non-exponential factor due, probably, to steric hindrance, in the very crowded situation, decreasing solvation of the transition state. The *trans*-1,2-diester has a rather large activation energy and non-exponential factor. If the compound is diaxial this may be explained by the buckling effect (see above), raising E and decreasing solvation. If the compound is diequatorial the relation of the two groups to each other is the same as in the *cis*-1,2-diester; the values of E and log A are not raised to the same extent, however. The *trans*-1,2-monoester values are essentially similar to the diester values except that the log A factor is lower by 0·36. On

[16] Cf. Newman, *op. cit.*, ref. 12, p. 31.
[17] Smith, Scrogham, and Stump, Amer. Chem. Soc. Meeting Abs., Sept. 1959, 36s.

a statistical basis the value might be expected to be 0·3 lower. With the *cis*-1,2-monoester, the activation energy and non-exponential factors are lower than for the diester. This may be due to less steric inhibition of solvation and possibly a special orientation of the transition state required for the hydrogen-bonding effect.

Alkaline Hydrolysis of Methyl Cyclohexanecarboxylate and the Methyl 4-t-Butylcyclohexanecarboxylates.—The work of Cavell, Chapman, and Johnson [3] may now be further discussed in relation to the acid-catalysed hydrolysis results and the conformations deduced therefrom. The rate coefficients for alkaline hydrolysis extrapolated to 90° are given in Table 3. In the absence of any steric effect of the 4-t-butyl group (see discussion of acid-catalysed hydrolysis, p. 2547) we can evaluate the polar effect (in log k units) of the equatorial 4-t-butyl group on the equatorial 1-ester group in the alkaline hydrolysis of methyl *trans*-4-t-butylcyclohexanecarboxylate. The value for " 1 : 1 " solvent at 90° is given by log $(29{\cdot}9 \times 10^{-2}/37{\cdot}6 \times 10^{-2}) = -0{\cdot}10$.

With methyl *cis*-4-t-butylcyclohexanecarboxylate it is necessary to consider a possible change in the polar effect of the t-butyl group and also the change in the steric effect of ring hydrogen atoms, on changing the ester group from an equatorial to an axial conformation. The sum of the changes in polar and steric effects is $\log_{10}(3{\cdot}60 \times 10^{-2}/29{\cdot}9 \times 10^{-2}) = -0{\cdot}92$. It is reasonable to assume that changing the ester group from the equatorial to the axial conformation causes a reduction in rate because of steric influences which are chiefly due to 3- and 5-axial hydrogen atoms. The Taft–Ingold assumption is that steric influences are the same in acid-catalysed hydrolysis as in alkaline hydrolysis.[18] On the assumption of no polar effect of the 4-t-butyl group in acid hydrolysis, the steric effect of the axial hydrogen atoms in methyl *cis*-4-t-butylcyclohexanecarboxylate as compared with the *trans*-compound is obtained from the rate coefficients for acid-catalysed hydrolysis as log $(5{\cdot}48 \times 10^{-4}/26{\cdot}1 \times 10^{-4}) = -0{\cdot}68$. Therefore the change in polar effect of the equatorial 4-t-butyl group in alkaline hydrolysis on changing the ester group to the axial conformation is $-0{\cdot}92 - (-0{\cdot}68) = -0{\cdot}24$, *i.e.*, the total polar effect is −0·34. This value is 3·4 times the value found when the ester group is in the equatorial conformation.

It is doubtful whether so large an increase is reasonable. In principle, however, this change may result from one of two separate effects or a combination of them. Either it is caused by a change in the intrinsic polar influence of the 4-t-butyl group, *i.e.*, a change in the Hammett σ value,[19] or it is caused by the axial ester group's being more susceptible to polar influence than the equatorial ester group. This corresponds to a change in the Hammett ρ value. If this situation is accepted as reasonable, whatever factors are responsible, then it is desirable to see whether the behaviour of the other esters can be understood on the basis of (*a*) steric effects on axial ester groups being 4·8 times larger than for equatorial groups in both alkaline hydrolysis and acid hydrolysis, and (*b*) the changes in polar effect with conformation being similar to those observed with the 4-t-butyl ester.

Alkaline Hydrolysis of Dimethyl Cyclohexanedicarboxylates.—In the " 1 : 3 " solvent, the rate coefficient for an equatorial ester group in alkaline hydrolysis is $67{\cdot}3 \times 10^{-2}$, and for an axial group $67{\cdot}3 \times 10^{-2}/4{\cdot}80 = 14{\cdot}0 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$. Therefore the rate coefficient for the *trans*-1,4- and *cis*-1,3-diester with two equatorial groups reacting independently is $134{\cdot}6 \times 10^{-2}$, the average observed value being 332×10^{-2} l. mole^{-1} sec.$^{-1}$. This means that the polar effect of an ester group is responsible for an increase in rate by a factor of 2·6, or 0·42 in log units. For *trans*-1,3- and *cis*-1,4-compounds the calculated rate coefficient is $81{\cdot}4 \times 10^{-2}$ and the average observed value is $147{\cdot}5 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$, giving a factor of 1·81, or 0·26 in log units. These two factors are not very different and do not fit in with the supposed great differences in polar effect of the equatorial 4-t-butyl group as exerted on equatorial and axial ester groups.

[18] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.
[19] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 184.

As an alternative the extreme view may be taken that there is negligible change in the polar effect of the 4-t-butyl group as between the equatorial and axial ester groups. The difference in rate coefficient for alkaline hydrolysis between methyl *trans*- and *cis*-4-t-butylcyclohexanecarboxylate would then be due entirely to the difference in steric effect of the ring hydrogen atoms on the equatorial and axial ester groups. This view involves rejecting, in this situation, the Taft–Ingold assumption concerning the similarity of transition states and steric effects in acid-catalysed and alkaline hydrolysis.

The Arrhenius parameters in alkaline and acid hydrolysis for the *cis*- and *trans*-4-t-butyl esters suggest that the Taft–Ingold assumption may indeed be incorrect in this case. For acid-catalysed hydrolysis a comparison of the *cis*- and *trans*-4-t-butyl esters shows that a change from *trans*- to *cis*- causes a small increase in activation energy and a *decrease* in the non-exponential term, and this appears to be due to " classical " steric hindrance. In alkaline hydrolysis,[3] however, the change from *trans*- to *cis*- causes a large increase in activation energy and an *increase* in the non-exponential term.* This may be caused by an increase in the steric hindrance to solvation of the transition state in the *cis*- as compared with the *trans*-compound. If this explanation is correct, then the change in solvation in going from the initial state to the transition state is evidently more important in alkaline than in acid hydrolysis.

If we take this view, the change in steric effect of ring hydrogen atoms when the ester group is changed from equatorial to axial conformations changes k by a factor of 8·3 in alkaline hydrolysis for the " 1 : 1 " solvent. If this factor is applied to the " 1 : 3 " solvent the rate coefficient for the equatorial ester group is $67{\cdot}3 \times 10^{-2}$ and that for the axial ester group is $8{\cdot}1 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$.†

For the dimethyl *trans*-1,4- and *cis*-1,3-esters in the absence of polar effects the rate coefficient would be $134{\cdot}6 \times 10^{-2}$. The average rate coefficient is 332×10^{-2} l. mole^{-1} sec.$^{-1}$ and this corresponds to the polar effect of ester group on ester group increasing the rate by a factor of 2·6 (the same value as if the Taft–Ingold view is accepted). For the dimethyl *cis*-1,4- and *trans*-1,3-esters the rate coefficients in the absence of polar effects should be $(67{\cdot}3 + 8{\cdot}1) \times 10^{-2} = 75{\cdot}4 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$ in each case. The observed average value is $147{\cdot}5 \times 10^{-2}$, and therefore polar effects increase the rates by a factor of ~2·0. The difference between the factors of 2·6 and 2·0 may be explained if orientation of the dipoles in the ester groups gives slightly different polar effects. The logarithm of the mean of these factors, +0·36, may be taken as an approximate measure of the polar effects of the ester group in the alkaline hydrolysis. Thus the polar effect of the t-butyl group in this reaction is −0·10 (see above) and that of the ester group is +0·36, *i.e.*, the relative polar effect of the two groups (ignoring the difference in sign) is ~3·5. According to Jaffé [14] the σ_m values are −0·12 for t-butyl and +0·32 for the ester group. These are in the ratio of ~3 (σ_m values are approximate measures of inductive effects). The relative polar effect of the groups in the cyclohexane ring as derived above is thus approximately the same as their relative inductive effect in the benzene ring.

The alkaline hydrolysis of methyl cyclohexanecarboxylate, methyl *cis*- and *trans*-4-t-butylcyclohexanecarboxylate, and dimethyl 1,4- and 1,3-cyclohexanedicarboxylates can

* For the *trans*-compound, $E = 11{\cdot}0$ kcal./mole and $\log A = 6{\cdot}1$; for the *cis*-compound, $E = 13{\cdot}6$ kcal./mole and $\log A = 6{\cdot}7$.

† The factor cannot be derived directly for the " 1 : 3 " solvent since the methyl 4-t-butylcyclohexanecarboxylates are too insoluble for kinetic study. The validity of assuming that the relative reactivity of equatorial and axial ester groups in alkaline hydrolysis is the same in the two solvents was tested by measuring the rate coefficients for dimethyl *trans*- and *cis*-1,4-cyclohexanedicarboxylates in the " 1 : 1 " solvent at 14·8°. The values are $3{\cdot}62 \times 10^{-2}$ and $1{\cdot}72 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$, respectively, the ratio of these being 2·1. Values calculated from Cavell, Chapman, and Johnson's work [3] for the " 1 : 3 " solvent are in the ratio of 2·3. The ratio of the rate coefficients for the *trans*- and *cis*-esters depends on (*a*) the relative reactivity of equatorial and axial ester groups in the absence of polar effects of substituents, and (*b*) the change in the mutual polar effects of the ester groups as between *eq-eq* and *eq-ax* conformations. The agreement (to within 8%) of the above values of the ratio suggests that (*a*) and (*b*) are about the same in the two solvents.

thus be explained fairly well in the following terms: (*a*) the conformations based on the results for acid-catalysed hydrolysis, (*b*) steric effects giving the equatorial and axial ester groups a relative reactivity of 8·3 at 90°, (*c*) polar effects of the t-butyl and methoxycarbonyl groups which are roughly independent of conformation and are related to the inductive effect of the groups in the benzene system.

The 1,2-*Diesters in Alkaline Hydrolysis.*—We consider first the *cis*-1,2-diester which has the unambiguous conformation of equatorial-axial ester groups. The rate coefficient in acid-catalysed hydrolysis for the compound with the groups reacting independently would be $52{\cdot}1 \times 10^{-4}$, and the observed value is $4{\cdot}32 \times 10^{-4}$, *i.e.*, there is a reduction in rate by a factor of 0·083 or −1·08 in log units. This is probably a measure of the mutual steric effect of the two ester groups in acid-catalysed hydrolysis and, if the Taft–Ingold view is accepted, it can be applied to the alkaline hydrolysis results. For alkaline hydrolysis the rate coefficient calculated for this compound with the groups reacting independently is either $81{\cdot}4 \times 10^{-2}$ or $75{\cdot}4 \times 10^{-2}$ (see discussion of *trans*-1,3- and *cis*-1,4-diesters, above and the observed value is $23{\cdot}8 \times 10^{-2}$, giving a reduction factor of 0·29 or 0·32, *i.e.*, −0·53 or −0·50 in log units, depending on the value taken for the calculated rate; the polar effect derived by subtracting −1·08 is +0·55 or +0·58 respectively. These values are rather larger than the value of ~0·36 obtained for the polar effect in *trans*-1,3- or *cis*-1,4-diesters but are quite reasonable since the two groups are now much closer together.

If the *trans*-1,2-diester is diaxial (the conformation which gives the better explanation for the results of acid-catalysed hydrolysis) then the calculated rate coefficient for acid-catalysed hydrolysis is $18{\cdot}06 \times 10^{-4}$; the observed value is $4{\cdot}62 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, giving a factor of 0·26 or −0·59 in log units. It is supposed that this value measures the steric effect produced by the buckling of the cyclohexane ring (see p. 2550). For alkaline hydrolysis the calculated rate coefficient is either $28{\cdot}2 \times 10^{-2}$ or $16{\cdot}2 \times 10^{-2}$ (see discussion of *trans*-1,3- and *cis*-1,4-diesters above, p. 2551) and the observed value is $51{\cdot}3 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$; the factor is thus 1·82 or 3·16, *i.e.*, +0·26 or +0·50 in log units. If the measure of the steric effect based on the acid-catalysed hydrolysis may be applied, the polar effect in alkaline hydrolysis is either +0·85 or +1·09. If the *trans*-1,2-diester is supposed to have the diequatorial conformation (following Cavell, Chapman, and Johnson [3]) the polar effect in alkaline hydrolysis is +0·85.

Whatever assumption is made about the conformation of the *trans*-1,2-diester, the polar effect is thus calculated to be somewhat larger than that for the *cis*-1,2-diester (+0·55 or +0·58) and is considerably larger than the value for *trans*-1,3- and *cis*-1,4-diesters (+0·36). In the light of this discussion it does not seefn possible to reach firm conclusions about the conformation of the *trans*-1,2-diester.

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490. *The Chelates formed by Tin(II) with Certain Amino-polycarboxylic Acids.*

By T. D. Smith.

pH titration and polarographic work with tin(II) chloride and EDTA, confirmed by use of 1,2-cyclohexylenediaminetetra-acetic acid, indicates formation of a range of chelate compounds. Polarography of tin(II)–EDTA may provide a method of analysis for the metal. The results are briefly discussed in relation to those for other metals.

In order to assess the factors involved in the formation of stable chelates of cations with small negative partial molal entropies the behaviour of tin(II) with a number of amino-carboxylic acids has been studied. Few investigations of the stability constants have been carried out [1] but studies of the tin(II) chelates involved in analytical work indicate that tin(II) complexes may be formed with a wide range of organic ligands.

Titration curves for the tin(II)–ethylenediamine-*NNN'N'*-tetra-acetic acid (EDTA) system are shown by Fig. 1. An inflexion occurs in curve C when a, the number of equivalents of alkali added per g.-atom of metal ion, is two. This corresponds to the formation of a 1 : 1 chelate: $Sn^{2+} + H_2Y^{2-} \rightleftharpoons SnY^{2-} + 2H^+$ where Y^{4-} is the tetra-negative anion of the amino-carboxylic acid. Above pH ~7 the curve rises less steeply and is presumably due to the liberation of further quantities of hydrogen ion: $SnY^{2-} + H_2O \rightleftharpoons [SnY{\cdot}OH]^{3-} + H^+$, though this equilibrium does not account quantitatively for the deviation from ideal behaviour. Curve D illustrates that a second ligand is not added. When the molar ratio of tin(II) to EDTA disodium salt was 1 : 0·5 no precipitation occurred on titration. The chelate formed must be Sn_2Y, the reaction, $Sn^{2+} + \frac{1}{2}H_2Y^{2-} = \frac{1}{2}Sn_2Y + H^+$, leading to an inflexion at $a = 1$. It is assumed therefore that the chelate is readily hydrolysed.

The ultraviolet absorption spectra of the tin(II) chelate of EDTA depends markedly on the pH of the solution (see Fig. 2). The absorbance increases steadily up to pH ~2·80; then a large increase occurs; the absorbance is unchanged from pH 4·0 to pH ~7·0, whereafter it again increases; finally, at pH 10·3 it decreases. The effect of pH on the ultraviolet spectrum of EDTA is also shown. The changes in absorption of the tin(II) chelate solution cannot be explained in terms of the variation of absorption of the reagent itself, and indeed at pH 2·80 the absorption of the chelate solution is greater than that of the reagent. The changes in absorbance of the chelate above pH 7·0 are paralleled by changes in the pH titration curves which have been ascribed to hydrolysis.

A similar series of changes takes place in the case of the tin(II) chelate of 1,2-cyclohexylenediaminetetra-acetic acid. The variation in the absorption of the reagent itself with pH is similar to that shown by Fig. 2.

Further evidence of the range of existence and stability of the tin(II) chelates may be obtained from polarographic data. Typical polarograms for solutions of tin(II) and EDTA at various pH's are shown in Fig. 3. At pH 2·80 a wave is obtained at about −0·80 v. At pH's above 2·80 the wave at −0·80 v disappears, leaving one at −0·20 v which has substantially the same height over the pH range of 1·8—7·5. At pH ~9·0 the wave at −0·2 v decreases in height and a new wave appears at −0·08 v.

A study of the polarographic behaviour in the presence of the other reagents mentioned substantiates these observations. For example, the tin(II) chelate of 1,2-cyclohexylenediaminetetra-acetic acid gives waves at −0·14 v and −1·03 v, and at pH >9·50 the height of the wave at −0·14 v decreases.

Solutions of tin(IV) in the presence of EDTA and 1,2-cyclohexylenediaminetetra-acetic acid over the pH range 1·50—9·50 gave no polarographic response. The wave

[1] "Stability Constants," Part I and Part II (L. E. Sutton), *Chem. Soc. Special Publ. No.* 7, 1957.

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obtained at −0·20 and −0·14 v for tin(II) may thus result from the oxidation of the tin(II) to the tin(IV), though the invariance of $E_{\frac{1}{4}}$ and wave-height over the range of pH remains unexplained. The oxidation of tin(II) at about −0·2 v in the presence of the amino-carboxylic acids is similar to that obtained in acetate and tartrate media.[2]

FIG. 1. pH *Titration of the tin*(II)–EDTA *system.* Ratio tin(II) : H_2Y^{2-}; A, 0 : 1; B, 1 : 0·5; C, 1 : 1; D, 1 : 2.

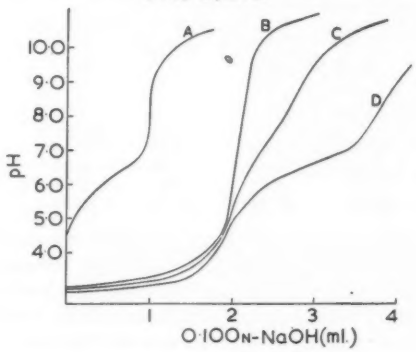


FIG. 2. *Spectra of solutions containing* 10^{-4}M-*tin*(II) *and* 10^{-4}M-EDTA.
1, pH 2·80; 2, pH 4·40; 3, pH 7·80; 4, pH 9·30; 5, pH 10·30.
Spectra of solutions containing 10^{-4}M-EDTA.
A, pH 2·80; B, pH 7·90; C, pH 9·40; D, pH 10·30.

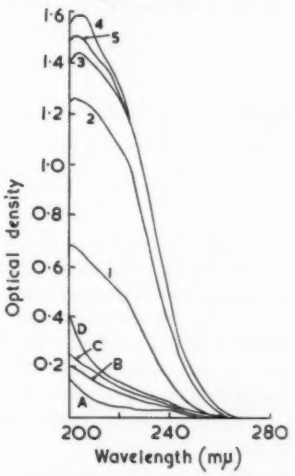


FIG. 3. *Polarographic responses of solutions containing* 10^{-3}M-*tin*(II), 10^{-2}M-EDTA, 0·1M-*sodium perchlorate, and* 0·005% *of gelatin.*
1, pH 2·80; 2, pH 4·15; 3, pH 9·25; 4, pH 10·20.

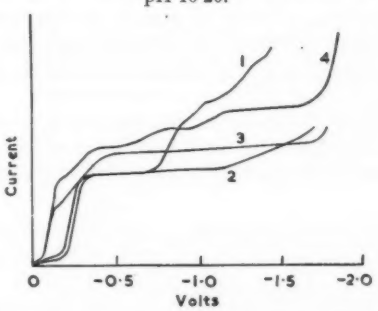
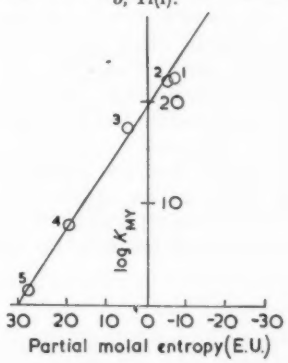


FIG. 4. *Correlation of stability constants with partial molal entropies of the cation.*
1, Sn(II); 2, Hg(II); 3, Pb(II); 4, Ag(I); 5, Tl(I).



The curve at −0·20 v for tin(II) in EDTA at pH 4·5 may be suitable for tin(II) analysis and, though this is dealt with in detail here, a study of the collected data [2] indicates that the wave may be suitable for the quantitative analysis of tin(II) in the presence of other metals. However, both polarographic and spectrophotometric observations indicate that between pH 3·6 and 6·0 the tin(II) chelate of EDTA has the composition SnY^{2-}.

[2] Lingane, "Electroanalytical Methods," Interscience Publ. Inc., New York, 1953.

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The polarographic response of tin(II) solutions in the presence of EDTA provides a convenient method for measuring the concentration of tin(II). The addition of thorium ion in the presence of an acetate buffer, in amount equivalent to that of tin(II) chelate, at pH 4·00 resulted in the partial displacement of tin(II). It was established that, under the solution conditions, the wave-height at −0·47 v was proportional to the concentration of tin(II). The tin(II) concentration of a number of solutions containing stannous ion, EDTA, 0·02M-acetate, and 0·10M-sodium perchlorate at pH 4·00 was measured by noting the height of the wave at −0·47 v due to free tin(II), and the stability constant for the tin(II) chelate was computed by using the known value for the thorium chelate.[3] The exchange reaction may be represented: $SnY^{2-} + Th^{4+} \rightleftharpoons Sn^{2+} + ThY$. The stability constant K_{SnY} for the tin(II) chelate is given by the expression

$$\log K_{SnY} = \log K_{ThY} \cdot \frac{[SnY^{2-}][Th^{4+}]}{[Sn^{2+}][ThY]}$$

The equilibrium concentrations are shown in the Table.

Total concns. (10^{-3}M) of Sn(II) & Th(IV)	1·00	2·00	1·50	0·50
$[Sn^{2+}]$ (10^{-3}M)	0·78	1·48	1·20	0·39
$[SnY^{2-}]$ (10^{-3}M)	0·21	0·51	0·30	0·11
log K	22·09	22·28	21·98	22·09

In contrast to earlier considerations[4,5] which dealt with large stability constants arising from metal ions of large negative partial molal entropies the stability constant for the tin(II) chelate is large, though the partial molal entropy for tin(II) is considerably more positive. As shown in Fig. 4, correlation of partial molal entropies of the metal ions with the log K of their chelates with EDTA indicates that the ions of thallium(I), silver(I), lead(II), tin(II), and mercury(II) comprise a separate group; this correlation is a quantitative expression of the general similarity in chemical properties of these ions. Unfortunately no further quantitative data on the behaviour of tin(II) with other organic ligands are available.

However, for combination of the metal ions of this group with olefins a further refinement is obtained in that, whilst silver and mercury form complexes with olefins, tin(II), lead(II), and thallium(I) do not.

The stereochemistry of the ligand is important in determining the relative positions of the ions in this group. A study[1] of the chelating agents of the general formula $R{\cdot}N(CH_2{\cdot}CO_2H)_2$ indicates that the log K for the mercury(II) chelates is much smaller than those of lead(II). On the other hand in a study of ligands of the type $(HO_2C)_2N{\cdot}[CH_2]_n{\cdot}N(CO_2H)_2$ the log K's for mercury(II) are found to be larger than those for the corresponding lead(II) chelate, which is little affected by change in n and consequently in ring size.

It is possible that, for the log K of the mercury(II) chelate to exceed that for lead(II), as in the case of EDTA, the stereochemistry must be suitable for the formation of sp-linear bonds, whilst lead(II) and tin(II) are able to form p^3d hybridised bonds with a greater variety of stereochemistry of the ligand.

Experimental

pH *Titrations*.—The technique was essentially that described previously.[4]

A 0·0100M-solution of tin(II) was prepared by dissolving "AnalaR" stannous chloride in 1·00 ml. of approximately 9N-hydrochloric acid contained in a stoppered flask. The flask was gently heated to effect dissolution, then cooled; after dilution the contents were transferred to a 1-l. flask and made up to volume. To determine the acidity of the stock solution due to

[3] Schwarzenbach, Gut, and Anderegg, *Helv. Chim. Acta*, 1954, **37**, 937.
[4] Foreman and Smith, *J.*, 1752, 1957.
[5] Smith, *J. Inorg. Nuclear Chem.*, 1959, **11**, 314.

the hydrochloric acid the procedure was repeated, but stannous chloride was omitted: an aliquot part of this solution was titrated with base.

In the pH titration of tin(II)–EDTA solutions the acidity due to the hydrochloric acid was subtracted from the total figure to obtain that generated by chelate formation. Fresh stock solutions of tin(II) were prepared for each experiment.

The polarographic measurements were made with a Tinsley polarograph and an H-type cell, one arm consisting of a saturated calomel electrode in a thermostat at 20° ± 0·1°. Calibration waves were derived for the tin(II) ion by variation of concentration. In all cases the tin(II) solutions containing the chelating agents were set aside for 12 hr. at a given pH for equilibration. The absorption spectra of solutions of tin(II) chelates were recorded with a Unicam S.P. 500 spectrophotometer.

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491. *Steric Inhibition of Hydrogen-bonding in Solutions of 4-Methyl-2,6-di-t-buiylphenol.*

By J. J. WREN and P. M. LENTHEN.

Low-resolution infrared spectra show that 4-methyl-2,6-di-t-butylphenol has a slight but measurable tendency to form hydrogen bonds with bases. In dilute solutions of this compound in basic solvents three species have been detected, one free and two hydrogen-bonded. The bonded species are believed to contain hydrogen atoms oriented in and out of the plane of the benzene ring.

Two peculiarities of hydroxyl stretching absorption in spectra of 2,6-di-t-alkylphenols (so-called " hindered phenols " [1]) are widely recognized. One is the high frequency, and the other is that little or no absorption attributable to self-association can be detected in concentrated solutions.[2,3] In spectra of 4-methyl-2,6-di-t-butylphenol dissolved in basic solvents a third peculiarity has been found, namely, the coexistence of one absorption attributable to free hydroxyl groups and two others attributable to hydrogen-bonded

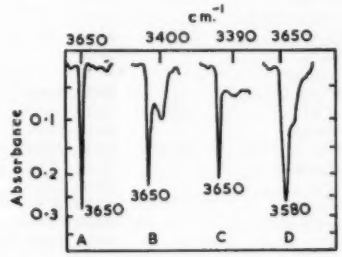


FIG. 1. *Spectra of* 0·272M-*solutions of* 4-*methyl*-2,6-*di-t-butylphenol in* (A) *cyclohexane*, (B) *diethyl ether*, (C) *triethylamine, and* (D) *dioxan. Cells* 0·1 *mm., pure solvents in reference beam.*

hydroxyl groups. These occur in the regions 3650, 3610—3580, and 3500—3390 cm.$^{-1}$, respectively.

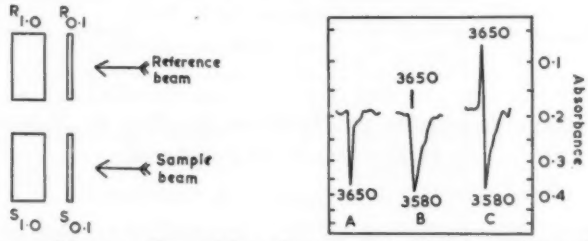
Solutions of this phenol in four non-basic solvents gave a single, sharp peak in the hydroxyl stretching region at approximately 3650 cm.$^{-1}$ (Table, Fig. 1A). The apparent molar absorptivity (ε_A) in each case was about 100, and Beer's law was obeyed even in the most concentrated solutions (0·5M).

Solutions in diethyl ether also gave a sharp peak at 3650 cm.$^{-1}$ which obeyed Beer's

[1] Stillson, Sawyer, and Hunt, *J. Amer. Chem. Soc.*, 1945, **67**, 303.
[2] Coggeshall, *J. Amer. Chem. Soc.*, 1947, **69**, 1620; Sears and Kitchen, *J. Amer. Chem. Soc.*, 1949, **71**, 4110; Hughes, Martin, and Coggeshall, *J. Chem. Phys.*, 1956, **24**, 489; Puttnam, *J.*, 1960, 486.
[3] Bellamy and Williams, *Proc. Roy. Soc.*, 1960, *A*, **255**, 22.

law, but ε_a was only 75. As Fig. 1B shows, this peak was accompanied by a shoulder at 3600 cm.$^{-1}$ and a broad subsidiary peak at 3400 cm.$^{-1}$ which also obeyed Beer's law. Solutions in cineole and triethylamine gave similar results. Solutions in dioxan (Fig. 1D) gave superficially different spectra: shoulders at 3650 and 3400 cm.$^{-1}$ flanked a peak at 3580 cm.$^{-1}$. However, in dioxan–carbon tetrachloride (1 : 10 v/v) the main peak was at 3650 cm.$^{-1}$, with shoulders at 3580 and 3400 cm.$^{-1}$. The peaks at 3650 and 3580 cm.$^{-1}$ were successfully resolved in a differential experiment (Fig. 2).

FIG. 2. *Differential infrared spectrophotometry. Two* 0·1 *mm. cells and two* 1·0 *mm. cells* ($R_{0\cdot1}$, $S_{0\cdot1}$ *and* $R_{1\cdot0}$, $S_{1\cdot0}$, *respectively*) *were arranged as indicated, and the slit width was nominally* 60 μ. *The cells were filled as follows*:



Spectrum A. $R_{0\cdot1}$: *cyclohexane.* $R_{1\cdot0}$ *and* $S_{1\cdot0}$: *dioxan.* $S_{0\cdot1}$: 0·272M-*phenol in cyclohexane.*
Spectrum B. $R_{0\cdot1}$ *and* $R_{1\cdot0}$: *dioxan–cyclohexane* (10 : 1 v/v). $S_{0\cdot1}$ *and* $S_{1\cdot0}$: *dioxan–*0·272M-*phenol in cyclohexane* (10 : 1 v/v).
Spectrum C. $R_{0\cdot1}$: 0·272M-*phenol in cyclohexane.* $R_{1\cdot0}$: *dioxan.* $S_{0\cdot1}$ *and* $S_{1\cdot0}$: *dioxan–*0·272M-*phenol in cyclohexane* (10 : 1 v/v).

Findings for other basic solvents were qualitatively similar (see Table). Apparently the peaks found at highest frequency in direct experiments on benzene, ethyl acetate, acetonitrile, and acetone were produced by overlapping of peaks near 3650 and 3610 cm.$^{-1}$.

Hydroxyl stretching absorption in solutions of 4-*methyl-*2,6-*di-t-butylphenol.*

Solvent	Ref. 3 [a]	ν (cm.$^{-1}$) Direct [b]	Differential [c]	ε_a [d]	Fraction not bonded [e]	
Hexane	3655	3650		101	(1·00)	(1·00)
Cyclohexane ...		3650		97	(1·00)	(1·00)
CCl_4	3650	3650		98	(1·00)	(1·00)
$CHCl_3$		3650		106	(1·00)	(1·00)
Benzene		3640	(3650), 3610, 3500			0·60
EtOAc		3620, 3480 [f]	(3650), 3610, 3470 [f]			0·83
MeCN	3627	3630, 3390 [f]	(3650), 3610, 3390 [f]			0·86
Acetone		3610, 3390 [f]	(3650), 3590, 3410 [f]			0·73
Et_2O	3651	3650, 3600, [f] 3400	(3650), 3600, 3400	75	0·71	0·72
Dioxan		3650, [f] 3580, 3400	(3650), 3580, 3430 [f]	39	0·37	0·39
Pr^i_2O		3650, 3480	(3650), 3610, 3480	88	0·84	0·88
Cineole		3650, 3590, [f] 3400		81	0·77	
Pyridine		3650, [f] 3400	(3650), 3600, [f] 3400	31	0·30	0·29
NEt_3		3650, 3600, [f] 3390		72	0·69	

[a] ±1 cm.$^{-1}$. [b] ±10 cm.$^{-1}$. [c] ±10 cm.$^{-1}$. Solvents mixed with 1/10 vol. of cyclohexane (cf. Fig. 2). [d] From direct experiments (3650 cm.$^{-1}$). [e] First column: ε_a/105. Second column: from differential experiments. [f] Shoulder.

The peak at *ca.* 3650 cm.$^{-1}$ is attributed to the free hydroxyl group, in which the hydrogen atom lies in a t-butyl " basket," in the plane of the benzene ring.[4] From the literature [5,6] it is clear that the other peaks should be attributed to hydrogen-bonded species which, existing in dilute solutions, must be of the simple bimolecular type,

[4] Ingold, *Canad. J. Chem.*, 1960, **38**, 1092.
[5] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 2nd edn., 1958, ch. 6; Sheppard in " Hydrogen Bonding," ed. Hadži, Pergamon, London, 1959, p. 85.
[6] Pimentel and McClellan, " The Hydrogen Bond," Freeman, San Francisco, 1960, ch. 3.

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Phenol · · · Solvent. Only two such species can be visualized, with the hydrogen atom lying respectively in and out of the plane of the benzene ring. It is not possible to argue from known facts which frequency should be attributed to which species. The out-of-plane species lacks resonance-stabilization, but molecular models show that it is less hindered than the in-plane species.

It is interesting that, in dilute solutions in carbon tetrachloride, 2-t-butylphenols with 6-substituents smaller than t-butyl give two free-hydroxyl stretching peaks. Goddu [7] has attributed these to " in-plane " species with the hydrogen atom oriented towards the 2- or the 6-position.

Fractions representing the proportion of our phenol that is not associated with solvent at room temperature are shown in the Table. They represent the maximum proportion, because any overlap of the adjacent bands would increase the magnitude of ε_a at 3650 cm.$^{-1}$. There is good agreement between fractions from direct and differential experiments.

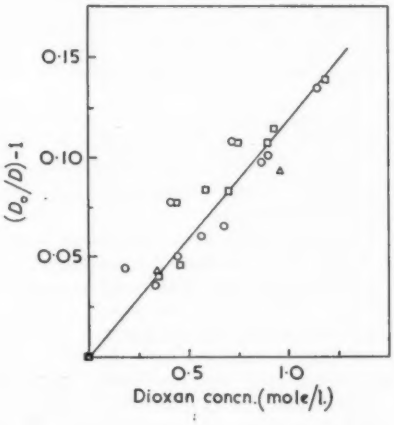

FIG. 3. *Determination of K for the equilibrium,* phenol + dioxan $\rightleftharpoons$ phenol · · · dioxan, *in carbon tetrachloride.*

□ 20°, ○ 50°, phenol 0·0242 mole/l. △ 20°, phenol 0·0454 mole/l.

The basic solvents are listed in the Table in probable order of increasing basicity.[6,8] That this is not the order of increasing association with the phenol must be due to steric hindrance. Thus pyridine, which is less basic than triethylamine but offers less steric hindrance to hydrogen-bond formation, associates twice as much. Dioxan and cineole present an analogous contrast. Despite their great difference in basicity, diethyl ether and triethylamine associate about equally.

The equilibrium constant (K) for hydrogen-bond formation between our phenol and dioxan in dilute solutions in carbon tetrachloride has been determined at 20° and 50°. If the concentration of the phenol is relatively low, so that [dioxan] $\gg$ [phenol · · · dioxan], and if activities are assumed to be unity, K can be derived from the simple relations

$$K = \frac{[\text{phenol} \cdots \text{dioxan}]}{[\text{phenol}][\text{dioxan}]} = \frac{D_0 - D}{cD} = \frac{(D_0/D) - 1}{c},$$

where D_0 = absorbance at 3650 cm.$^{-1}$ of the phenol in CCl_4, D = absorbance at 3650 cm.$^{-1}$ of the same concentration of the phenol in CCl_4 containing dioxan, and c = concentration of dioxan.

Fig. 3 is a plot of $(D_0/D) - 1$ against c. The best straight line for the 20° points is shown ($K = 0{\cdot}12 \pm 0{\cdot}01$ l. mole^{-1}) but it is indistinguishable from that for the 50° points. Maximum values for the enthalpy and entropy change have been calculated from the

[7] Goddu, *J. Amer. Chem. Soc.*, 1960, **82**, 4533.
[8] Searles and Tamres, *J. Amer. Chem. Soc.*, 1951, **73**, 3704.

extremes of the standard error; *viz.*, from $K_{293} < 0{\cdot}12 + 0{\cdot}01$ and $K_{323} > 0{\cdot}12 - 0{\cdot}01$, $-\Delta H < 1100$ cal. mole^{-1} and $-\Delta S < 8{\cdot}1$. The values of K and $-\Delta H$ are lower than any quoted by Pimentel and McClellan [9] for comparable systems. (Lindberg [10] doubted his value, $-\Delta H = 300$, for 2,6-dimethoxyphenol.)

Data in the literature [2,3] generally show no evidence that one molecule of a 2,6-di-t-alkylphenol can associate with another, but four types of association could perhaps occur, by hydrogen-bonding of in-plane and out-of-plane hydrogen atoms with electrons on oxygen atoms or benzene rings. This might explain the low frequencies found by Bellamy and Williams [3] for solid (3627 cm.$^{-1}$) and liquid 4-methyl-2,6-di-t-butylphenol (3636 cm.$^{-1}$; cf. data on acetonitrile in the Table). Spectra of 4-methoxy-2,6-di-t-butylphenol [11] show a minor, broad peak at 3450 cm.$^{-1}$ which may be attributed to hydrogen-bonding with methoxyl oxygen.

The present work establishes that this phenol can associate with sterically less hindered bases but that its tendency to associate is remarkably slight. It is apparently the first hydroxylic compound found that is not quantitatively hydrogen-bonded in dilute solutions in basic solvents. This is a phenomenon recently discovered [12] for C:CH compounds, and which is just revealable for t-butyl alcohol by a differential experiment.

Experimental.—*4-Methyl-2,6-di-t-butylphenol.* This was Eastman " Tenox " " BHT," m. p. 70·5—71° (corr.) [lit.,[1] 70° (uncorr.)]. Purity was confirmed by the full spectrum.

Solvents. Hexane and di-isopropyl ether (technical grade), chloroform and diethyl ether (" AnalaR "), and cyclohexane and carbon tetrachloride (" Spectrosol ") were used without further purification.

Benzene, ethyl acetate, acetone, and pyridine (" AnalaR ") were passed through a column of Linde molecular sieve 5A before use.

Acetonitrile was fractionally distilled from P_2O_5, K_2CO_3, and P_2O_5 in that order. 1,4-Dioxan and cineole (eucalyptol) were fractionally distilled from lithium aluminium hydride, and triethylamine from sodium.

Infrared measurements. A small, double-beam spectrophotometer with sodium chloride optics was used (Perkin–Elmer " Infracord," model 137E). The slit width was automatically controlled except in differential experiments. Measurements were carried out at 20° ±2° or 50° ± 2°. A density correction was applied for carbon tetrachloride at 50°.

Frequency readings were calibrated by using the 3655 cm.$^{-1}$ peak of the phenol in hexane [3] and the 2925 cm.$^{-1}$ peak of polystyrene, and were reproducible to ±10 cm.$^{-1}$. Absorbance readings were measured on the assumption of zero absorbance at the minimum near 3720 cm.$^{-1}$: these proved more reliable than readings measured from other baselines. Apparent molar absorptivities (ε_a l. mole^{-1} cm.$^{-1}$) were calculated from these readings.

The spectra of all solvents were checked before use, and control experiments were made as rigorously as possible.

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[*Received, December 22nd,* 1960.]

[9] Ref. 6, appendices B and C.
[10] Lindberg, *Soc. Sci. Fennica, Comm. Phys.-Math.*, 1957, **20**, 1.
[11] Cook, Inskeep, Rosenberg, and Curtis, *J. Amer. Chem. Soc.*, 1955, **77**, 1672; Müller and Ley, *Chem. Ber.*, 1955, **88**, 601.
[12] Wojtkowiak and Romanet, *Compt. rend.*, 1960, **250**, 3980; Brand, Eglinton, and Morman, *J.*, 1960, 2526.

492. *Kinetic Studies of the Fluorene Series. Part I. The Acid-catalysed Solvolysis of 9-Diazofluorene.*

By KEITH D. WARREN.

The reaction has been studied in ethanol and in ethanol–water mixtures. Hydrochloric, perchloric, and picric acids were used as catalysts, and the effect of added salts was determined. Experiments with picric acid–lithium picrate buffers, and with a partially deuterated solvent, indicated that the reaction was general acid-catalysed.

A reaction mechanism is suggested in which attack of the solvated proton on the substrate is rate-determining and the fluorenyl carbonium ion is the active intermediate.

THIS work is preliminary to an investigation of the influence of substituents in the benzenoid rings on the rate of cleavage of the diazo-group from the 9-position of fluorene. Solvolysis of 9-diazofluorene in aqueous ethanol proves to be general acid-catalysed as is that of the closely related diphenyldiazomethane,[1] and contrasts with the specific acid-catalysed hydrolysis of diazoacetic ester.[2]

Order of Reaction.—The reaction in 93·8% (w/w) ethanol–water, with hydrochloric or perchloric acid as catalyst, is of first order with respect to 9-diazofluorene for at least 80% of its course. For values of [HCl] below 0·05M, the first-order rate constant, k_1, varies linearly with the stoicheiometric concentration of acid. With perchloric acid as catalyst, k_1 varies similarly. The specific rate constant, k_s (slope of the plot of k_1 against [$HClO_4$]) differs negligibly from the corresponding value for hydrochloric acid (Table 1). Both plots show a small zero-intercept on the acid-concentration axis, possibly associated with an irregular rate variation at very low acid concentrations (cf. diphenyldiazomethane [1]).

TABLE 1. *Solvolysis of 9-diazofluorene in 93·8% (w/w) ethanol–water at 25·00°.*

Catalyst: HCl. k_s = 3·93 (min.$^{-1}$ mole^{-1} l.)

10^2[$C_{13}H_8N_2$] (M)	1·00	1·00	0·50	1·00	0·50	1·00	1·00	0·50
10^2[HCl] (M)	0·48	0·96	0·96	1·49	1·49	1·99	2·47	2·47
10^2k_1 (min.$^{-1}$)	1·50	3·05	3·20	5·05	5·20	6·65	8·53	8·40
10^2[$C_{13}H_8N_2$] (M)	1·00	1·33	0·50	0·50	0·50	0·50	0·50	
10^2[HCl] (M)	2·95	3·55	4·18	8·25	13·53	16·90	21·65	
10^2k_1 (min.$^{-1}$)	10·4	13·3	15·3	37·6	70·5	90·0	124	

Catalyst: $HClO_4$. [$C_{13}H_8N_2$] = 0·0050M, k_s = 4·00 (min.$^{-1}$ mole^{-1} l.)

10^2[$HClO_4$] (M)	0·59	1·48	2·47	3·60	5·00	10·05	15·11	20·15
10^2k_1 (min.$^{-1}$)	1·93	5·56	9·30	14·3	20·5	49·4	93·0	134

TABLE 2. *Variation of rate with solvent composition.*

Catalyst: HCl; Temp.: 25·00°

% EtOH (w/w)	100	98·5	93·8	87·8	81·75	76·9
k_s (min.$^{-1}$ mole^{-1} l.)	45·6	12·2	3·93	4·03	4·10	4·44

Above 0·05M the value of k_s increases progressively with acid concentration, rather more so for perchloric acid than for hydrochloric acid. Since, below about 0·4M, the Hammett acidity function, h_0, varies linearly with acid concentration,[3] this is probably due to a primary salt effect, the addition of comparable amounts of electrolytes producing similar increases (Table 3).

Dependence of Rate on Solvent Composition.—When the water content of the solvent is increased from zero, k_s initially falls sharply, showing later a much smaller gradual rise (Table 2). This effect closely parallels the variation of the acidity function with solvent

[1] Roberts and Watanabe, *J. Amer. Chem. Soc.*, 1950, **72**, 4869.
[2] Gross, Steiner, and Krauss, *Trans. Faraday Soc.*, 1936, **32**, 877.
[3] Baines and Eaborn, *J.*, 1956, 1436.

composition,[4] although the initial inhibition of the reaction can be ascribed simply to the replacement of the reactive ethoxonium ions by the less active hydroxonium ions.

Salt Effects.—The reaction, catalysed by hydrochloric or perchloric acid, shows a large positive salt effect. With about 0·02M-acid, the progressive addition of lithium chloride or lithium perchlorate, up to 0·20M, results in a regular increase in the rate, the latter being somewhat more effective (Table 3). A plot of $\log_e (k_c/k_0)$ against [Added Salt] (k_c and k_0 being the first-order rates with and without added salt, respectively) is reasonably linear, as expected for a reaction between an ion and a neutral molecule.

TABLE 3. *Salt effects.*

[HCl] = 0·0210M; Solvent and temp. as in Table 1

Added Salt	LiCl	LiCl	LiCl	LiCl	LiCl	$LiClO_4$	$LiClO_4$	$LiClO_4$	$LiClO_4$	$LiClO_4$
10^2[Added Salt] (M)	2·41	5·56	8·45	11·70	19·45	2·43	5·66	8·89	12·30	19·80
$\log_e k_c/k_0$	0·080	0·165	0·218	0·257	0·430	0·050	0·254	0·308	0·458	0·628

$[HClO_4]$ = 0·0215M

Added Salt	$LiClO_4$	$LiClO_4$	$LiClO_4$	$LiClO_4$	LiCl	LiCl	LiCl	LiCl
10^2[Added Salt] (M)	3·70	9·04	14·20	19·35	4·10	9·45	14·68	19·85
$\log_e k_c/k_0$	0·070	0·214	0·372	0·583	0·040	0·166	0·305	0·500

No measurable reaction was observed between 9-diazofluorene and either lithium salt in the absence of an acid catalyst. Since the salt effect of lithium perchlorate exceeds that of lithium chloride, and perchlorate ion is not involved in the solvolysis (see p. 2563), it is most improbable that chloride ions take part in the rate-determining stage, or that the salts act otherwise than by increasing the dielectric constant of the medium.

Similar large salt effects occur in the solvolysis of diphenyldiazomethane.[1]

Energy of Activation.—The values of the Arrhenius energies of activation, E_A, relating to each catalyst, agree well for both temperature intervals (Table 4), suggesting that in each case catalysis is due to oxonium ions. Hydrochloric acid is completely dissociated [5]

TABLE 4. *Variation of rate with temperature.*

Solvent: 93·8% (w/w) ethanol–water

	Catalyst: HCl			Catalyst: $HClO_4$		
Temp.	25·00	35·00	45·00	25·00	35·00	45·00
k_s (min.$^{-1}$ mole^{-1} l.)	3·93	10·9	26·7	4·00	10·6	26·0

E_A (25—35°) = 18,150 ± 600 cal., $\log_{10} A$ = 13·72 ± 0·70, $\Delta S^{\ddagger}$ = −4·85 ± 1·5 e.u. E_A (35—45°) = 17,450 ± 600 cal.

in 93·8% (w/w) ethanol–water, and complete dissociation would be expected for perchloric acid. In this solvent the hydroxonium ion probably predominates over the ethoxonium ion, and the temperature variation of E_A is insufficient to imply a composite catalysis. The entropy of activation, $\Delta S^{\ddagger}$, is consistent with rate-determining proton transfer.

Catalysis by Picric Acid.—With picric acid alone as catalyst, the plot of k_1 against the stoicheiometric concentration of acid shows increasingly large upward deviations from linearity. For 0·04M-acid, k_s is already 30% greater than the value at infinite dilution (which approximates to k_s for hydrochloric and perchloric acids and represents oxonium ion catalysis only) whilst for hydrochloric and for perchloric acid deviations are negligible (Tables 1 and 5).

In the solvent used picric acid is considerably dissociated: extrapolations from literature data [6] give values of 1·62 and 2·08 for pK_a. General acid catalysis could not therefore be detected in the normal manner, but for four concentrations of picric acid the effect of added lithium picrate has been studied. The value of the ionic strength at each acid concentration was kept constant by adding lithium perchlorate; salt effects were thus largely

[4] Braude and Stern, *J.*, 1948, 1976, 1982.
[5] Bezman and Verhoek, *J. Amer. Chem. Soc.*, 1945, **67**, 1330.
[6] Goldschmidt, *Z. phys. Chem.*, 1928, **132**, 257; Gross, Jamock, and Patat, *Monatsh.*, 1933, **63**, 124

eliminated, but the rate increase caused by lithium picrate was never less than three times that due to lithium perchlorate (Table 5). Lithium picrate alone had no catalytic action.

Since this former rate increase seems too great to constitute a salt effect, catalysis by undissociated picric acid is indicated, with a catalytic constant $k_{s(\mathrm{H\ Picr})}$, slightly greater than that, $k_{s(H_3O^+)}$, of the oxonium ion. The abnormal increase in rate with increasing acid concentration, or the addition of lithium picrate, results from the rising concentration of

TABLE 5. *Catalysis by picric acid.*

Solvent and temp. as in Table 1.

10^2[picric acid] (M)	1·00	1·25	1·25	2·01	2·50	2·50	2·50	2·50	2·50
10^2[Li picrate] (M)	—	5·00	—	—	—	—	1·67	3·33	5·00
10^2[$LiClO_4$] (M)	—	—	5·00	—	—	5·00	3·33	1·67	—
10^2k_1 (min.$^{-1}$)	4·12	6·05	8·25	8·70	11·1	13·0	13·9	15·3	17·8
10^2[picric acid] (M)	3·02	3·50	3·50	4·02	5·05	5·05	5·05	5·05	5·05
10^2[Li picrate] (M)	—	—	5·00	—	—	—	1·67	3·33	5·00
10^2[$LiClO_4$] (M)	—	5·00	—	—	—	5·00	3·33	1·67	—
10^2k_1 (min.$^{-1}$)	14·2	19·2	25·6	20·5	28·4	31·6	34·0	36·0	37·0

undissociated picric acid. This surprising result ($k_{s(\mathrm{H\ Picr})} > k_{s(H_3O^+)}$) was also reached [1] for the diphenyldiazomethane solvolysis: it may be significant that in 93·8% (w/w) ethanol–water the hydroxonium ion is the simple H_3O^+, a much weaker proton donor [4] than the highly solvated $H^+,4H_2O$ present in mainly aqueous solutions.

Isotope Effect.—Partial deuteration of the aqueous ethanol used as solvent leads to rapid isotopic exchange with the catalysing acid. For the solvent composition chosen (hydrochloric acid catalyst), the specific rate was reduced to 73% of its former value (Table 6), consistent with rate-determining proton transfer and general acid catalysis.

TABLE 6. *Isotope effect.*

Temp.: 25·00°

	Solvent: 87·8% (w/w) EtOH–H_2O				Catalyst: HCl; Solvent: 87·8% (w/w) EtOH–D_2O			
10^2[HCl] (M)	1·91	2·89	3·69	4·58	1·91	2·89	3·69	4·58
10^2k_1 (min.$^{-1}$)	7·10	10·6	13·9	17·4	5·90	8·20	10·5	12·8

$k_s(D_2O)/k_s(H_2O) = 0·73$

Reaction Products.—The reaction, catalysed by hydrochloric acid, produced appreciable amounts of 9-chlorofluorene (Table 7): in the product-determining step chloride ion competes more effectively with ethanol than with the more nucleophilic water. When chloride ion is added as lithium chloride the production of 9-chlorofluorene is favoured, possibly owing to the effective removal of water in solvating the lithium ion. With perchloric or picric acid, or their salts, present in the reaction mixture, *in the absence of chloride ion*, no loss of acid, due to the participation of the anion in the product-determining stage, is observed.

TABLE 7. *Side-product formation.*

Temp.: 25·00°. $[C_{13}H_8N_2] = 0·005$M

	Solvent: 100% ethanol				Solvent: 98·5% (w/w) ethanol–water			
10^2[HCl] (M)	1·15	1·90	2·49	3·80	1·14	2·47		3·76
% conversion of substrate into 9-chlorofluorene	44	43	45	46	26	29		36

Solvent 93·8% (w/w) ethanol–water

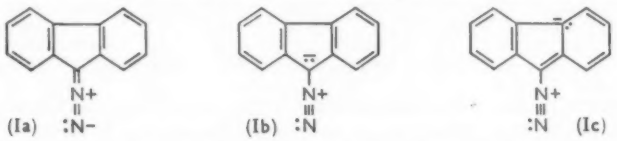
10^2[HCl] (M)	8·25	13·53	16·90	2·10	2·10	2·10	2·10	2·10
10^2[LiCl] (M)	—	—	—	2·41	5·56	8·45	11·70	19·45
% conversion of substrate into 9-chlorofluorene	14	19	22	19	27	29	33	39

Product runs, with perchloric acid as catalyst, in 93·8% (w/w) ethanol–water, gave 9-ethoxyfluorene and 9-hydroxyfluorene, in ratio 5 : 3, and a small amount of unidentified red gum. Similar runs, with hydrochloric acid, gave, in addition, 9-chlorofluorene, which

was also found, with about equal amounts of 9-ethoxyfluorene, when ethanol was used as solvent.

Mechanism of Reaction.—The solvolysis shows general acid catalysis and proton transfer from the general acid, HA,(H_3O^+, $EtOH_2^+$, or picric acid) to the substrate is therefore rate-determining. The residue whence the proton is detached (H_2O, EtOH, or picrate ion) is thus involved in the transition state (II).

9-Diazofluorene may be considered as a resonance hybrid of the contributing canonical forms (Ia) and (Ib). The former is stabilised by conjugation of the diazo-group with both benzenoid rings, and the latter by the predisposition of cyclopentadiene systems [7] to contribute structures such as (Ic), the formal negative charge being distributed over the ring. It is postulated that the solvolysis is initiated by attack of the solvated proton (or other general acid) on the 9-carbon atom, the substrate being represented as structure (Ib).



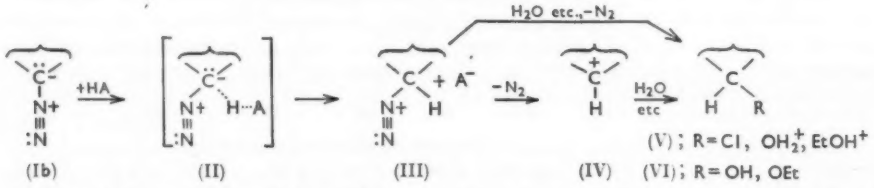
(Ia) (Ib) (Ic)

Confirmatory evidence from the rate-dependence in the region wherein h_0 and the hydrogen-ion concentration diverge, was unobtainable because of the rapidity of the reaction. Melander and Myhre [8] have, however, concluded that it should not thus be possible to distinguish between an AS_E2 reaction and one involving a fast pre-equilibrium. The expected rate dependence for AS_E2 processes remains uncertain.[9]

Previously investigated AS_E2 reactions have involved subsequent rapid reaction of the protonated substrate with water or another base, Y. An alternative possibility (not distinguishable by kinetic form) is rapid decomposition of the protonated substrate to a further intermediate, X^+, which then reacts rapidly with a base. (The reaction sequence resembles the A-1 mechanism, but the first step is rate-determining.) It is proposed to call this mechanism AS_E2'.

$$AS_E2\left\{\begin{array}{ll} S + HA \longrightarrow SH^+ + A^- & \text{(slow)} \\ SH^+ + Y \longrightarrow \text{Products} & \text{(fast)} \end{array}\right. \qquad AS_E2'\left\{\begin{array}{ll} S + HA \longrightarrow SH^+ + A^- & \text{(slow)} \\ SH^+ \longrightarrow X^+ & \text{(fast)} \\ X^+ + Y \longrightarrow \text{Products} & \text{(fast)} \end{array}\right.$$

There arises then the question whether the fluorenyldiazonium ion (III), first formed, decomposes unimolecularly (AS_E2'), yielding the fluorenyl carbonium ion (IV) (which would then react with water or ethanol), or loses nitrogen simultaneously with the attack of the nucleophile in a bimolecular step (AS_E2). Since these alternatives arise after the rate-determining step, kinetic evidence is inapplicable, but the following considerations suggest that the reaction proceeds *via* the carbonium ion (IV).



(Ib) (II) (III) (IV)

(i) Participation of chloride ion in the initiating step is excluded. Its appearance in the products must then be due to attack on either the diazonium ion (III) or the carbonium

[7] Wheland, "Resonance in Organic Chemistry," John Wiley and Co., New York, 1955, pp. 136, 347.

[8] Melander and Myhre, *Arkiv Kemi*, 1959, **13**, 507.

[9] Gold, *Ann. Reports*, 1959, **56**, 46.

ion (IV). Since the nucleophilic strength of chloride ions in processes of similar charge-type appears much greater than that of ethanol or water,[10] bimolecular reaction of the diazonium ion should lead mainly to 9-chlorofluorene, which is stable under reaction conditions. Production of this as a *minor* component thus suggests that chloride ion competes with water and ethanol for the carbonium ion. Perchlorate ion is less nucleophilic than ethanol [10] and would be expected not to intervene in this stage.

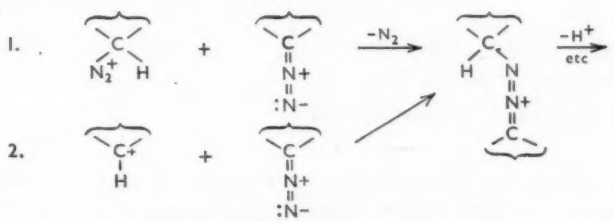
(ii) The relatively high proportion of 9-hydroxyfluorene formed (chloride ion absent) in 93·8% solvent, probably originates in the greater nucleophilic strength of water (as compared with ethanol) in such media. The appreciable production of 9-chlorofluorene (chloride ion present) is paralleled in the S_N1 solvolysis of *pp'*-dimethyldiphenylmethyl chloride in aqueous acetone [11] (small additions of sodium azide produce considerable amounts of *pp'*-dimethyldiphenylmethyl azide).

(iii) The products of reactions involving comparable diazonium ions necessitate loss of nitrogen and carbonium-ion formation, *e.g.* the Demjanov rearrangement and the action of nitrous acid on primary amines [12] to produce some branched-chain products.

(iv) Although some 9-substituted fluorenes undergo S_N2 attack, *e.g.* 9-bromofluorene with iodide ion in acetone,[13] in more polar solvents steric factors should favour S_N1 reaction. Coplanarity (favoured for the bimolecular transition complex) of the bonds attached to the 9-carbon atom, is inhibited by the rigidity of the tricyclic fluorene framework. Nucleophilic attack thus more probably involves the planar carbonium ion.

Furthermore, resonance stabilisation of the diazonium ion (III) is meagre, but the carbonium ion (IV) should be stabilised by conjugative mesomerism with the aromatic rings (cf. benzyl carbonium ion). The carbonium ion, which is about as stable as the diphenylmethyl ion and more stable than the benzyl ion,[14] is the postulated intermediate [15] in the conversion of 9-hydroxyfluorene and sodium azide into phenanthridine by strong acids.

(v) Staudinger and Kupfer,[16] using a large excess of 9-diazofluorene in about 80% (w/w) ethanol–water with hydrochloric acid as catalyst, found small amounts of fluorenone ketazine in the products. Either of the schemes shown could explain this. Mechanism (1) requires attack of 9-diazofluorene on the diazonium ion at a point remote from the carbon–nitrogen bond. This implies improbably close approach of the two fluorene residues, whereas scheme (2) is not thus hindered.



Interpolation from the present results shows that the hydrogen-ion catalysed solvolysis of 9-diazofluorene in 93·8% ethanol–water is about twelve times slower than that of diphenyldiazomethane. This difference probably originates in the electron affinity of cyclopentadiene systems whereby somewhat greater resonance stabilisation [*e.g.* structure

[10] Hughes, Ingold, and Pocker, *Chem. and Ind.*, 1959, 1282; Swain and Kaiser, *J. Amer. Chem. Soc.*, 1958, **80**, 4089.
[11] Bateman, Hughes, and Ingold, *J.*, 1940, 974.
[12] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 486.
[13] Dickinson and Eaborn, *J.*, 1959, 3547.
[14] Deno, Jaruselski, and Schriesheim, *J. Org. Chem.*, 1954, **19**, 155.
[15] Arcus and Evans, *J.*, 1958, 789.
[16] Staudinger and Kupfer, *Ber.*, 1911, **44**, 2197.

(Ic)] is derived than is possible for diphenyldiazomethane. This accords with the comparably greater reactivity [17] of fluorenone, as compared with benzophenone, in oximation, which requires electron accession to the 9-position.

Diazoacetic ester which shows specific acid catalysis [2] in hydrolysis contrasts with the fluorene and diphenylmethane derivatives. This difference may be due to the low resonance stabilisation of diazoacetic ester itself and the rather small difference between those of the diazonium and carbonium ions thence derived. This should facilitate proton transfer and either retard the heterolysis of the diazonium ion (*A*–1) or result in a slow bimolecular substitution (*A*–2.)

Experimental

Reagents.—Solutions of 9-diazofluorene [18] were freshly prepared for each run. Stock solvents were prepared by the addition of the requisite volumes of water to absolute ethanol,[19] and stock hydrochloric acid by passing dry hydrogen chloride into the appropriate solvent. The 93·8% (w/w) solvent had d_4^{20} 0·8077. Stock perchloric acid was obtained from the 72% product by its addition to absolute ethanol so as to yield a solution of the acid in 93·8% (w/w) ethanol–water. Anhydrous lithium chloride was prepared by heating reagent-grade material at 120° for 3 hr., and anhydrous lithium perchlorate and lithium picrate according to Roberts and Watanabe.[1]

Products.—The reaction products [in 93·8% (w/w) ethanol–water; perchloric acid as catalyst] were fractionally crystallised from light petroleum, the first crop yielding 9-hydroxyfluorene as white needles, m. p. 156—157° (corr.), and the residues yielding 9-ethoxyfluorene as white needles (from aqueous alcohol), m. p. 53° (corr.). With hydrochloric acid as catalyst the products contained, in addition to the above, 9-chlorofluorene, produced also (with 9-ethoxyfluorene) when absolute ethanol was used as solvent. Isolation proved unsatisfactory for its estimation which was done by back titration of the reaction mixture, giving chloride ion loss during a run. 9-Chlorofluorene was shown to be negligibly solvolysed thereby.

Kinetic Runs.—These were carried out in a twin-limbed vessel held in a mechanical shaker. This was connected to a manometer consisting of a pair of microburettes, and the nitrogen evolved was measured at constant pressure. The reaction vessel was immersed in a thermostat tank, maintained at 25·00°, 35·00°, or 45·00° ± 0·03°, heating being controlled by a conventional mercury–toluene regulator. The reaction system was allowed 20 min. to equilibrate before each run was started, thus minimising corrections for evolution of solvent vapour.

The first-order rate constants were calculated by using the usual equation and were reproducible to within ±3% (±5% for $k_1 > 0{\cdot}5$). The energies of activation are believed to be correct to within ±0·6 kcal.

The University, Glasgow, W.2. [*Received, November 18th*, 1960.]

[17] Dickinson and Eaborn, *J.*, 1959, 3641.
[18] Nenitzescu and Solomonica, *Org. Synth.*, Coll. Vol. II, p. 496.
[19] Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1104.

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493. *Magnetic Perturbation of Singlet–Triplet Transitions. Part VI.* Octa-1,3,5,7-tetraene.*

By D. F. Evans.

The singlet–triplet absorption spectrum (induced by oxygen under pressure) of octa-1,3,5,7-tetraene in chloroform solution, and the first singlet–singlet absorption of the pure vapour have been measured. A simple preparation of octa-1,3,5,7-tetraene is described.

The induced singlet–triplet absorption spectra of ethylene, butadiene, and hexa-1,3,5-triene in the presence of oxygen under pressure have been reported.[1] The present paper is concerned with the next member of the series, octa-1,3,5,7-tetraene. Although this

* Part V, *J.*, 1961, 1987.
[1] Evans, *J.*, 1960, 1735.

very unstable compound has previously been prepared by two different routes,[2,3] a third, and in some ways more convenient, preparation was devised. The vapour-phase singlet–singlet absorption spectrum of octa-1,3,5,7-tetraene was also measured.

Experimental

Octa-1,3,5,7-tetraene.—Octa-2,4,6-trien-1-ol was prepared in good yield by reduction of octa-2,4,6-trienal with sodium borohydride in methanol; this method seems more convenient than that given in ref. 4. It was slowly distilled under *ca.* 0·1 mm. of oxygen-free nitrogen through a tube packed with aluminium oxide (desiccating agent) which was heated at 290°. The products were condensed in a trap kept at −78°. After warming to room temperature, the crude solid octa-1,3,5,7-tetraene was dissolved in isopentane, and the solution was dried (Na_2SO_4) and cooled at −78°. The resulting, almost colourless crystals were filtered on a low-temperature filter, washed with cold isopentane, and quickly dried in a stream of nitrogen (yield *ca.* 40%). The product was characterised by its infrared spectrum in carbon disulphide solution, and its ultraviolet absorption spectrum in 2,2,4-trimethylpentane solution, which were in good agreement with those reported by Woods and Schwartzman [2] and Lippincott *et al.*[3] According to the latter workers, octa-1,3,5,7-tetraene probably has an all-*trans*-structure. Since octa-1,3,5,7-tetraene polymerizes very rapidly in the solid state, solutions were prepared immediately the compound was dry, and physical measurements were made within 1—2 hr.

The vapour-phase singlet–singlet absorption spectrum was obtained by using evacuated 1-mm. or 1-cm. quartz cells attached by a graded seal to a bulb containing a few crystals of octa-1,3,5,7-tetraene.

Ultraviolet and visible spectra were measured on a Perkin–Elmer 4000 recording spectrophotometer.

Results and Discussion

Singlet–Triplet Transitions.—The spectrum (Fig. 1) closely resembles those obtained [1] for butadiene and hexa-1,3,5-triene. It is clear that two transitions are present and they can similarly be assigned as involving the first and the second triplet level of octa-1,3,5,7-tetraene. The positions of the 0,0 bands (13,750, 21,550 cm.$^{-1}$) and absorption maxima (*ca.* 17,000, *ca.* 23,000 cm.$^{-1}$) for the two transitions follow the trend found with butadiene and hexa-1,3,5-triene. The separation between the 0,0 bands of the first and the second transition shows a remarkable constancy in the series (7920 cm.$^{-1}$ butadiene; 7860 cm.$^{-1}$ hexa-1,3,5-triene; 7800 cm.$^{-1}$ octa-1,3,5,7-tetraene).

Singlet–Singlet Transition.—The first singlet–singlet transition (V_1–N) of octa-1,3,5,7-tetraene in the vapour phase is shown in Fig. 2. The bands are much sharper than those observed for gaseous butadiene [5] or hexa-1,3,5-triene.[6] All the main bands can be satisfactorily accounted for by two vibrational frequencies (1640 and 1240 cm.$^{-1}$; see Table), which may be tentatively assigned as symmetrical " double- " and " single- " bond stretching frequencies of the upper singlet state. The vapour-phase spectrum of hexa-1,3,5-triene, measured photographically by Price and Walsh,[6] also shows two vibrational intervals, at 1615 and 1230 cm.$^{-1}$. Although these authors considered the possibility that two vibrational frequencies of the V_1 state were involved, they thought it more likely that two geometrical isomers of hexa-1,3,5-triene were present (no bands involving multiple quanta of the 1230 cm.$^{-1}$ vibration could be detected). The present results for octa-1,3,5,7-tetraene suggest that the first alternative is, in fact, probably correct. The absence of multiple quanta of the 1230 cm.$^{-1}$ vibration is probably due largely to the breadth of the hexa-1,3,5-triene bands, together with the difficulty of detecting weak, diffuse bands photographically.

[2] Woods and Schwartzman, *J. Amer. Chem. Soc.*, 1949, **71**, 1396.
[3] Lippincott, Feairheller, and White, *J. Amer. Chem. Soc.*, 1959, **81**, 1316.
[4] Reichstein, Ammann, and Trivelli, *Helv. Chim. Acta*, 1932, **15**, 261.
[5] Price and Walsh, *Proc. Roy. Soc.*, 1940, *A*, **174**, 222.
[6] Price and Walsh, *Proc. Roy. Soc.*, 1946, *A*, **185**, 182.

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The absorption spectrum of octa-1,3,5,7-tetraene in 2,2,4-trimethylpentane (Fig. 2) or hexane solution [2] shows no trace of the two vibrational intervals found in the gas phase.

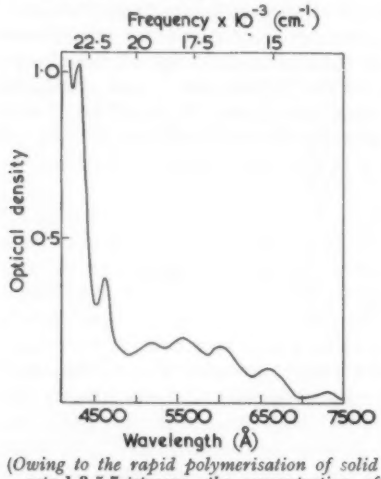
V_1–N bands of octa-1,3,5,7-tetraene in the vapour phase. (The positive deviations at high frequencies may arise partly from the neglect of anharmonicity. There is evidence for a further vibrational frequency of ca. 350 *cm.*$^{-1}$.)

Frequency (cm.$^{-1}$)	Analysis	Deviation (cm.$^{-1}$) (calc. − meas.)	Frequency (cm.$^{-1}$)	Analysis	Deviation (cm.$^{-1}$) (calc. − meas.)
35,520	0,0		39,660	1640 + 2 × 1240	−20
~35,860 (i)			40,030	2 × 1640 + 1240	+10
36,770	1240	−10	40,460	3 × 1640	+20
37,170	1640	−10	41,270	2 × 1640 + 2 × 1240	+10
~37,540 (i)			41,670	3 × 1640 + 1240	+10
38,010	2 × 1240	−10	42,040	4 × 1640	+40
38,410	1640 + 1240	−10	~42,410 (i)		
38,820	2 × 1640	−20	42,860	3 × 1640 + 2 × 1240	+60
~39,200 (i)			43,270	4 × 1640 + 1240	+50
			43,670	5 × 1640	+50
			~43,990 (i)		

(i) = Inflection.

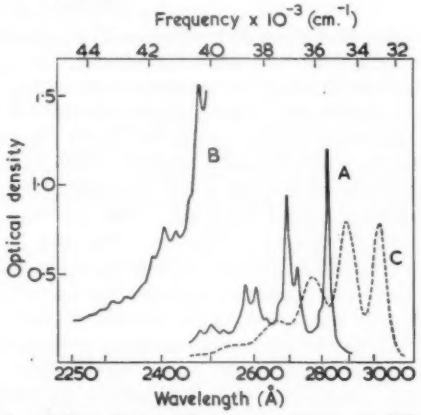
Owing to the effect of the solvent in broadening the bands, only a single interval of *ca.* 1500 cm.$^{-1}$ is observed, which is presumably composite. It seems very likely that the " characteristic " vibrational interval of 1400—1500 cm.$^{-1}$ found in the electronic spectra

FIG. 1. *Light absorption of oxygen at* 130 *atm. dissolved in a chloroform solution of octa-*1,3,5,7*-tetraene* (5·2*-cm. cell*).



(*Owing to the rapid polymerisation of solid octa-*1,3,5,7*-tetraene, the concentration of the solution was not determined.*)

FIG. 2. *First singlet–singlet absorption spectrum of octa-*1,3,5,7*-tetraene in the vapour state and in solution.*



A, *Vapour (saturated vapour pressure at* 29°) (1*-mm. cell*). B, *Vapour (saturated vapour pressure at* 29°) (1*-cm. cell*). C, *Solution in* 2,2,4*-trimethylpentane.*

(*Owing to the rapid polymerization of solid octa-*1,3,5,7*-tetraene, the concentration of the solution was not determined. Solution max. at* 33,140, 34,680, 36,130, 37,600, *and ca.* 39,200 (i) *cm.*$^{-1}$.)

of all types of polyenes in solution (and in butadiene vapour [5]) also involves two vibrational frequencies. Over 25 years ago, Hausser, Kuhn, and Seitz [7] showed the presence of two vibrational intervals (1570, 1230 cm.$^{-1}$) in the absorption spectra of diphenylpolyenes, polyenecarboxylic acids, and lycopene in rigid glasses at −196°. Although the bands are

[7] Hausser, Kuhn, and Seitz, *Z. phys. Chem.*, 1935, *B*, **29**, 391.

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rather broad, two vibrational intervals (*ca.* 1600 and *ca.* 1200 cm.$^{-1}$) can be detected in the previously reported [1] induced singlet–triplet transitions of gaseous butadiene.

The 0,0 band in the spectrum of octa-1,3,5,7-tetraene shifts to lower frequency by 2380 cm.$^{-1}$ as we go from the vapour phase to solution in 2,2,4-trimethylpentane. This solvent shift is slightly greater than the solvent shifts found for butadiene (1800 cm.$^{-1}$) and hexa-1,3,5-triene (2150 cm.$^{-1}$; hexane solution [6,8]), although the increase seems smaller than would be expected from the theoretical formula for solvent shifts derived by Longuet-Higgins and Pople.[9]

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[*Received, December 30th*, 1960.]

[8] Howton, *J. Org. Chem.*, 1949, **14**, 1.
[9] Longuet-Higgins and Pople, *J. Chem. Phys.*, 1957, **27**, 192.

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494. *The Kinetics of the Decomposition of Stannane on a Tin Surface.*

By S. F. A. KETTLE.

The kinetics of the decomposition of stannane between +50° and −50° have been studied in a static system. The rate is of first order in stannane above −10°, but kinetic anomalies appear below this temperature. These anomalies may be related to the appearance of the grey modification of tin on the catalytic surface. Oxygen acts as a catalyst at low partial pressures but at higher pressures inhibits the decomposition of stannane.

ALTHOUGH it is well known that stannane decomposes autocatalytically,[1] the only kinetic investigation was carried out by Tamarau.[2] He studied the decomposition on a tin surface in the range 35—100° and found the rate to be of the first order with respect to stannane, hydrogen not being adsorbed.[3]

The present work was carried out at lower temperatures, since below 13° grey tin is the stable allotrope [4] and its presence on the catalytic surface would presumably change the kinetics of the decomposition. Kinetic anomalies have indeed been found and may be explained largely, if not completely, by the presence of grey tin.

Tamarau found that oxygen prevented the decomposition of stannane and so worked with a pressure of less than 10^{-5} mm. in his apparatus. A further investigation of this effect shows that at very low pressures oxygen exhibits a catalytic effect.

The kinetics observed in the temperature range −10° to +50° were in reasonable agreement with those reported by Tamarau.[2] Plots of log (stannane pressure) against time were excellent straight lines, confirming that the decomposition is of the first order in stannane and unaffected by adsorption of hydrogen. The apparent activation energy was 10·9 ± 0·3 kcal. mole^{-1}, this being the average from three sets of runs. The results from two of these sets are shown in Figs. 1 and 2. A value of 9·1 kcal. mole^{-1} for the apparent activation energy was reported previously.[2]

At temperatures below −10° the catalytic surface was found to "age" quite rapidly. If the reaction vessel was kept at such a temperature for more than about six hours stannane did not decompose when admitted. Cooling to −50° for one hour caused the catalytic tin surface to fragment and fall to the bottom of the decomposition vessel. Subsequent *X*-ray analysis showed that although the fragments were largely

[1] Paneth, Haken, and Rabinowitsch, *Ber.*, 1924, **57**, 1891; Finholt, Bond, Wilzbach, and Schlesinger *J. Amer. Chem. Soc.*, 1947, **69**, 2692.
[2] Tamarau, *J. Phys. Chem.*, 1956, **60**, 610.
[3] Trapnell, *Proc. Roy. Soc.*, 1953, *A*, **218**, 566.
[4] Cohen and Van Lieshout, *Z. phys. Chem.*, 1935, **173**, 32.

white tin, they also contained some of the grey allotrope. The relative proportions are not significant since grey tin rapidly reverts to the white modification at room temperature.

A further indication of the "ageing" of the surface was shown by the non-reproducibility of kinetic results obtained below −10°. Two successive runs at the same temperature and initial pressure invariably gave different results. The disparity between the runs increased with the time interval between them.

Fig. 1 shows the results obtained from a series of runs in which the temperature was cycled. From *ca.* +50° to −10° the rate is of the first order in stannane, but from −10° to −30° it is almost constant, showing a slight negative temperature coefficient. The rate then rapidly decreases until, at −44°, it becomes zero. Raising the temperature in *ca.* 30° steps did not initiate decomposition until 40°, where, after an induction period

FIG. 1. *An Arrhenius plot of runs for which the temperature was "cycled," i.e., first reduced, then increased, and finally decreased again.*

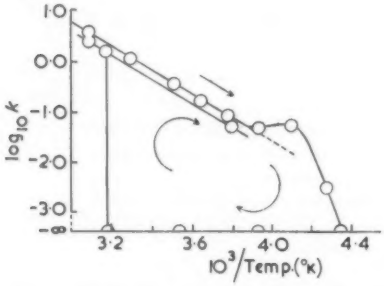


FIG. 2. *An Arrhenius plot which shows the ageing of a catalytic tin surface at ca. −10°.*

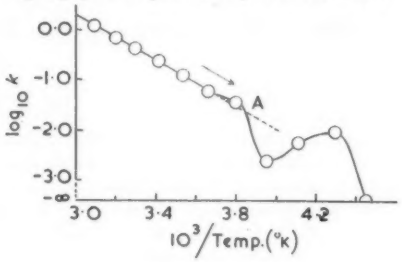


FIG. 3. *The effect of oxygen on the rate of decomposition of stannane.*

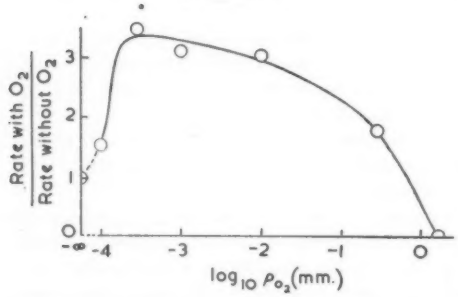
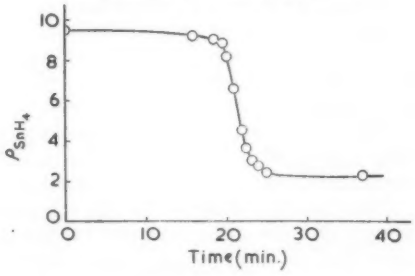


FIG. 4. *The decomposition of stannane at 20° in the presence of 1 mm. of oxygen.*



decomposition recommenced, the rate increasing until it was approximately that obtained earlier at about the same temperature. Further runs on the reactivated surface gave a plot of log k against T^{-1} parallel to that obtained before deactivation.

Fig. 2 provides a good example of the effect of the "ageing" of the catalytic surface at −10°. The decomposition vessel was held at point A (−10°) for two hours before the series of runs was continued. During the interruption the surface became a less active catalyst, but the newly deposited tin coating restored much of the activity, producing a rate with an apparent negative temperature coefficient.

It is evident that, because of the time-dependance of the reaction rates, Arrhenius plots obtained at low temperatures depend on the particular experimental procedure followed. Figs. 1 and 2 are two particular procedures chosen from many possible alternatives.

The most obvious explanation of the phenomena observed at low temperatures is that grey tin is catalytically inactive and that a surface changing from white to grey tin is more effective than white tin alone. There is, however, only indirect evidence of the amount of grey tin present. It may well be that only a very small extent of allotropic conversion is required to poison a catalytic white-tin surface completely. It was not found possible to decompose stannane at temperatures below −40°; it is reported[5] that the white ⟶ grey transformation is fastest at −48°.

Other effects may also be involved: (1) Cooling a thin tin film may cause surface strains or surface disruptions. Either might be expected to produce deviations from a simple kinetic behaviour. The fragmentation of a catalytic tin surface at −50° strongly suggests that these may be important factors. (2) It is a general phenomenon that at high pressures and/or low temperatures first-order rates for heterogeneous reactions with non-adsorbed products should become fractional and finally of zero order. This is associated with the increased adsorption of the reactants on to the catalytic surface. Such an effect may be occurring in the present research, but there is no evidence on the point.

The effect of added oxygen on the rate of decomposition of stannane at 20° is shown in Fig. 3. At a partial pressure of about 5×10^{-4} mm., oxygen shows its maximum catalytic effect, increasing the rate by a factor of 3—4. If we assume the tin surface to be perfectly smooth, at this pressure the ratio (surface tin atoms) : (oxygen atoms) is about 100 : 1. The catalytic effect of oxygen decreases as its partial pressure is further increased, until at 1 mm. it completely stops the decomposition of stannane. This observation finds application on the preparation of stannane, when, by having oxygen in the carrier-gas stream, the yield is increased. Presumably the autocatalytic decomposition of the product is inhibited.[6] It is also possible to store stannane at room temperature if it is mixed with oxygen.[6]

In those runs for which first-order kinetics were not obeyed initial rates were taken and are those plotted in Figs. 1—3. For Fig. 3 this procedure is not entirely satisfactory. Although Fig. 3 indicates that 1 mm. of oxygen "completely stops the decomposition of stannane," Fig. 4, which shows in detail the effect of 1 mm. of oxygen on a typical run at 20°, shows that the initial rate of zero corresponds to an induction period of about 15 min. After this induction period decomposition is very rapid but then virtually stops when about 20% of the stannane remains. Some features of the results obtained in the presence of oxygen appear to be almost independent of temperature and of oxygen concentration. An example is the cessation of decomposition when *ca.* 20% of the initial stannane remains. However, since these results are only roughly reproducible, no conclusions can safely be drawn.

Experimental

Stannane was made by the reduction of stannic chloride with lithium aluminium hydride in ether.[6] Stannane prepared by this method has been shown to give the purest tin yet obtained [7] (impurities $> 0{\cdot}00004\%$).

The kinetic apparatus, shown in Fig. 5, was made of Pyrex glass. After thorough evacuation and flaming, the decomposition vessel D was plated with tin by admitting stannane to a pressure of 10 cm. and initiating its decomposition with a flame. Further portions of stannane were then decomposed; when the tin surface was opaque it gave reproducible kinetic results. The decomposition was followed by the pressure change, indicated by the spiral gauge S. This gauge was sensitive to pressure changes of 0·1 mm. and its calibration (deflection *versus* pressure difference) was reproducible to ±2 mm. The dead volume of the kinetic apparatus was 1·1% of the total. A vacuum of less than 10^{-5} mm. in the wide-bore part of the apparatus was

[5] Cohen and Von Eijk, *Z. phys. Chem.*, 1899, **30**, 601.
[6] Emeléus and Kettle, *J.*, 1958, 2444.
[7] Brenner, Bierig, and Marsel, 17th Internat. Congr. Pure Appl. Chem., Münich, 1959, Paper A 226; also personal communication from W. Brenner.

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obtained by using two mercury pumps in series, backed by a rotary pump. The decomposition vessel was surrounded with a 5-l. Dewar flask containing water or acetone. The bath-liquid was stirred throughout all of the runs since the spiral gauge was unaffected by the slight vibration. An acetone-expansion thermoregulator controlled an electrical heater: for low-temperature runs the bath-liquid was cooled with a cold finger filled with solid carbon dioxide. The cold finger was lowered into the bath-liquid to a depth which caused the latter to cool

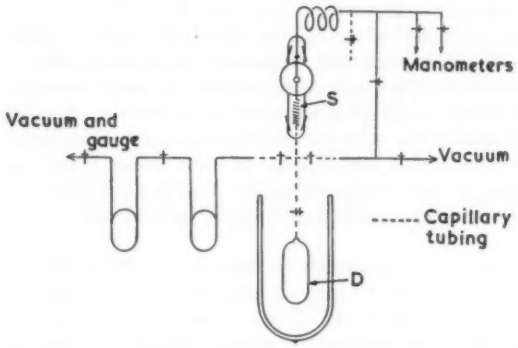

FIG. 5. *The kinetic apparatus.*

slowly; the electrical heater, controlled by the thermoregulator, then maintained the temperature. The bath-temperature was constant to $\pm 0{\cdot}1°$.

The oxygen used in the study of its effect on the decomposition of stannane was prepared by heating potassium permanganate in an evacuated flask, and was passed through a trap at $-196°$. Oxygen pressures were measured with a McLeod gauge; for very low pressures only the dead volume in the decomposition vessel was filled. When this oxygen was admitted to the decomposition vessel its pressure was reduced by a factor of 91. At the end of a run the decomposition vessel was evacuated to as low a pressure as possible. To reduce the effect of retained oxygen the next run was carried out with the oxygen pressure increased ten-fold.

The author is indebted to Professor H. J. Emeléus, F.R.S., C.B.E., at whose suggestion this work was carried out and who contributed greatly to it, and to the Department of Scientific and Industrial Research for financial support.

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NOTES.

495. *The Heat of Ionization of Some Substituted Anilines.*

By A. I. BIGGS.

IN a recent paper [1] the ionization constants of a number of substituted anilines and phenols at 25° were reported, the measurements being made by the spectrophotometric method. During some measurements to determine the effect of temperature on these ionization constants, it appeared that the difference in pK at 20° and at 40° was a linear function of the pK, already reported, at 25°. The pK values of phenol, aniline, and some substituted anilines have now been measured at 5° intervals between 20° and 40° and are given in the Table; we emphasize that these values are preliminary, being made in a rapid survey of the temperature effect. Over this short temperature range, and within the experimental accuracy, the pK values can be represented by: $pK = a + bt$, where the parameters can

[1] Biggs and Robinson, *J.*, 1961, 388.

be calculated by the method of least squares. Then the partial molal free energy and the enthalpy changes on ionization at 30° (the middle of our temperature range) are

$$\Delta\bar{G}^0 = 1{\cdot}387(a + bt)$$

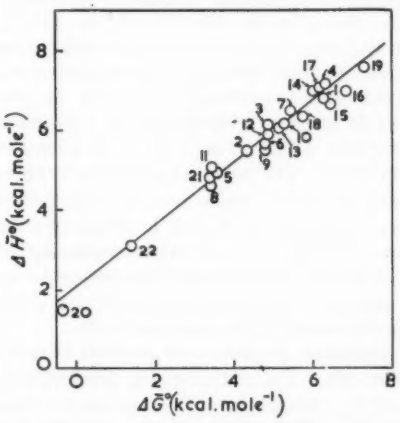
$$\text{and } \Delta\bar{H}^0 = -420{\cdot}5b$$

respectively, each in kcal. mole^{-1}.

p*K values of phenol, aniline, and some substituted anilines between 20° and 40°.*

No.	Compound *	20°	25°	30°	35°	40°
	Phenol	10·07	10·00	9·93	9·86	9·80
1	Aniline	$4{\cdot}68_6$	$4{\cdot}60_6$	$4{\cdot}52_7$	$4{\cdot}44_5$	$4{\cdot}36_6$
2	*o*-Fluoroaniline	3·25	3·20	3·12	3·05	3·00
3	*m*-Fluoroaniline	3·66	3·57	3·48	3·42	3·37
4	*p*-Fluoroaniline	4·73	4·65	4·56	4·48	4·39
5	*o*-Chloroaniline	2·70	2·64	2·58	2·53	2·46
6	*m*-Chloroaniline	3·60	3·52	3·46	3·39	3·33
7	*p*-Chloroaniline	4·07	3·98	3·92	3·83	3·76
8	*o*-Bromoaniline	2·57	2·53	2·47	2·42	2·35
9	*m*-Bromoaniline	3·60	3·53	3·46	3·39	3·34
10	*p*-Bromoaniline	3·95	3·88	3·80	3·73	3·66
11	*o*-Iodoaniline	2·61	2·55	2·49	2·43	2·37
12	*m*-Iodoaniline	3·66	3·59	3·52	3·45	3·38
13	*p*-Iodoaniline	3·87	3·79	3·71	3·65	3·58
14	*o*-Toluidine	4·52	4·44	4·36	4·27	4·18
15	*m*-Toluidine	4·80	4·72	4·64	4·56	4·48
16	*p*-Toluidine	5·16	5·07	4·99	4·90	4·83
17	*o*-Anisidine	4·61	4·52	4·45	4·35	4·28
18	*m*-Anisidine	4·30	4·23	4·15	4·08	3·99
19	*p*-Anisidine	5·44	5·34	5·24	5·16	5·08
20	*o*-Nitroaniline	−0·24	−0·26	−0·28	−0·30	−0·32
21	*m*-Nitroaniline	2·52	2·46	2·41	2·35	2·29
22	*p*-Nitroaniline	1·04	1·00	0·97	0·93	0·89

* The compounds used were the purest specimens available; they were either recrystallised from water (where possible) or distilled at low pressure in a stream of nitrogen, the middle fractions being taken.



Enthalpy change on ionization as a function of free energy change at 30°.

Plot of $\Delta\bar{H}^0$ against $\Delta\bar{G}^0$: 1, Aniline; 2—22, substituted anilines (see Table).

Enthalpy changes at 25° can also be calculated for comparison with values in the literature: for phenol we find 5·53 kcal. mole^{-1} compared with 5·60 given by Papée *et al.*[2] and 5·36 calculated from Binns's data.[3] For aniline at 25° we find $\Delta\bar{H}^0 = 6{\cdot}52$ kcal. mole^{-1} compared with 6·74 given by Zawidzki *et al.*[4]

[2] Papée, Canady, Zawidzki, and Laidler, *Trans. Faraday Soc.*, 1959, **55**, 1734.
[3] Binns, *Trans. Faraday Soc.*, 1959, **55**, 1900.
[4] Zawidzki, Papée, Canady, and Laidler, *Trans. Faraday Soc.*, 1959, **55**, 1738.

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A plot (see Figure) of $\Delta\bar{H}^0$ against $\Delta\bar{G}^0$, from the 30° data, shows that, in spite of considerable scatter, there is a definite indication of a linear relation between the two quantities. This possibility is worth more detailed investigation, partly because we believe that further work would improve the accuracy of the data given in the Table and also because there is a discrepancy between the enthalpy data for the toluidines derived from the pK values in the Table and the direct calorimetric measurements by Zawidzki *et al.*[4]

Papée *et al.*[2] found a linear relation between $\Delta\bar{H}°$ and $T/\Delta\bar{S}°$ for phenol, the cresols, and the xylenols, $\Delta\bar{H}°$ *increasing* with increasing $\Delta\bar{S}°$. Fernandez and Hepler's results [5] for the nitro- and chloro-phenols do not agree with this relation: for these phenols, $\Delta\bar{H}°$ varies approximately linearly with $\Delta\bar{S}°$ but the slope is in the opposite direction, $\Delta\bar{H}°$ *decreasing* with increasing $\Delta\bar{S}°$. This difference must also appear in a graph of $\Delta\bar{H}°$ against $\Delta\bar{G}°$. It seems, therefore, that there are $\Delta\bar{H}°$–$\Delta\bar{S}°$ and $\Delta\bar{H}°$–$\Delta\bar{G}°$ relations specific to the substituent group, methyl in one case and nitro or chloro in the other. This may well be true of the anilines and we suspect that further work on their pK values, over a wider temperature range, may reveal that the linear increase of $\Delta\bar{H}°$ with $\Delta\bar{G}°$ is only an approximation; the relationship may well contain a " fine structure " sensitive to the nature of the substituent groups.

The author thanks Professor R. A. Robinson for helpful discussion and interest.

Department of Chemistry, Petaling Jaya, Malaya. [*Received, September 27th*, 1960.]

[5] Fernandez and Hepler, *J. Amer. Chem. Soc.*, 1959, **81**, 1783.

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496. *Synthesis of Guanosine Diphosphate Glucose.*

By J. Baddiley, N. A. Hughes, and A. L. James.

The isolation of guanosine diphosphate glucose from *Eremothecium ashbyii* was reported recently from this laboratory.[1] Since the compound could not be separated from a considerable excess of guanosine diphosphate mannose and traces of guanosine diphosphate fructose, a chemical synthesis was desirable to confirm its identity. In view of the work of Khorana and his colleagues (cf. ref. 2), the most attractive route to this compound appeared to be the condensation of a guanosine-5′ phosphoramidate with a salt of α-D-glucopyranose 1-phosphate. Several guanosine-5′ phosphoramidates were synthesised and examined. The simple guanosine-5′ phosphoramidate and guanosine-5′ phosphoromorpholidate proved ineffective, probably owing to their lack of solubility in pyridine. However, guanosine-5′ *N*-cyclohexylphosphoramidate was more soluble and condensation occurred with the tri-n-octylammonium salt of α-D-glucopyranose 1-phosphate to give a product with the chromatographic properties expected for guanosine diphosphate glucose. At this time we became aware of work by Ueda and Ohtsuka [3] who synthesised guanosine diphosphate mannose by a similar route.

The synthetic product was purified by ion-exchange chromatography and isolated as its lithium salt. The nature of the product and its identity with the natural material were confirmed by chromatography in several solvent systems and by the following hydrolysis experiments. With dilute acid (pH 2) it gave D-glucose, guanosine-5′ phosphate, guanosine-5′ pyrophosphate, and inorganic phosphate; with ammonia it gave guanosine-5′ phosphate and α-D-glucopyranose 1,2-phosphate; treatment with the pyrophosphatase and 5′-nucleotidase of *Crotalus atrox* venom gave guanosine, α-D-glucopyranose 1-phosphate, and inorganic phosphate.

[1] Pontis, James, and Baddiley, *Biochem. J.*, 1960, **75**, 428.
[2] Moffatt and Khorana, *J. Amer. Chem. Soc.*, 1958, **80**, 3756.
[3] Ueda and Ohtsuka, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 389.

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By a similar method, with fructose 1-phosphate in place of glucose 1-phosphate, a small sample of guanosine diphosphate fructose was obtained. It is noteworthy that the rate of liberation of fructose from this compound by the action of dilute acid was appreciably faster than that of the natural guanosine diphosphate fructose, and it is tentatively assumed that the fructose–phosphate linkage in the natural compound is not through $C_{(1)}$ of the fructose.

Experimental

Evaporations were carried out under reduced pressure with the bath temperature of 35° or lower.

Hydrolyses of the synthetic nucleotides were performed as previously described;[1] results are quoted in the discussion.

Guanosine Diphosphate Glucose.—Cyclohexylamine (0·16 ml., 1·4 mmoles) and formamide (0·5 ml.), followed by dicyclohexylcarbodi-imide (280 mg., 1·35 mmoles) in t-butyl alcohol (2·0 ml.), were added to a solution of guanosine-5′ phosphate (75 mg., 0·21 mmole) in water (0·6 ml.). The resulting solution was heated at 80° for 10 hr. and left overnight at room temperature. Water (2 ml.) was added and the precipitated *NN′*-dicyclohexylurea was filtered off and washed with a little water. The combined filtrate and washings were extracted with ether (5 × 3 ml.) to remove any remaining carbodi-imide and the aqueous solution was evaporated to 0·5 ml. under reduced pressure. Addition of acetone (50 ml.) gave a white precipitate which, after 1 hr., was centrifuged, washed with acetone, dried, dissolved in water (1 ml.), and freeze-dried to a white powder (105 mg.). The product was shown by paper chromatography to be mainly guanosine-5′ *N*-cyclohexylphosphoramidate contaminated with a little diguanosine-5′ pyrophosphate (both as their *NN′N″*-tricyclohexylguanidinium salts); no guanosine-5′ phosphate was present. Solutions of the impure phosphoramidate (100 mg.) and tri-n-octylammonium α-D-glucopyranose 1-phosphate (400 mg., 0·65 mmole) in anhydrous pyridine (15 ml. and 10 ml. respectively) were mixed and set aside at 28° for 3 days. Pyridine was removed by evaporation; last traces were removed by the addition and subsequent evaporation of water (10 ml.). The residue was dissolved in water (10 ml.), and the pH of the solution was adjusted to 7·2 by the addition of 0·1N-lithium hydroxide solution before being passed through a column (40 cm. × 1 cm.) of Dowex-1(× 2) resin (200—400 mesh; chloride form). The column was washed with water until the washings showed no appreciable absorption at 255 mμ. The nucleotides were then removed by gradient elution, a hydrochloric acid–lithium chloride system being employed. The mixing chamber contained 0·0001N-hydrochloric acid (2 l.) and the reservoir contained 0·02N-hydrochloric acid (1 l.) and 0·4N-lithium chloride (1 l.). A linear gradient was employed at a rate of 0·5 ml./min., and fractions (10 ml.) were collected. The nucleotide content of each fraction was estimated from the absorption at 255 mμ. The nucleotides were eluted in four fractions (see below):

Fraction	Tube number	Contents	Nucleotide present (mmoles)
1	48—58	α-D-glucopyranose 1-phosphate and guanosine-5′ phosphate	0·014
2	62—67	guanosine-5′ *N*-cyclohexylphosphoramidate and guanosine-5′ phosphate	0·003
3	69—75	diguanosine-5′ pyrophosphate	0·013
4	133—146	guanosine diphosphate glucose	0·041

The pH of fraction 4 was adjusted to 6·8 with 0·5N-lithium hydroxide solution, and the solution was concentrated to 2 ml. Addition of acetone–ethanol (9 : 1; 100 ml.) gave a white precipitate which was centrifuged, washed with acetone–ethanol, and finally dried *in vacuo* to give the *lithium salt* of guanosine diphosphate glucose as a very hygroscopic grey-white powder (28 mg.). Elementary analysis indicated the compound to be heavily hydrated and efforts to obtain the anhydrous compound resulted in extensive decomposition (Found: N, 9·9; P, 8·4. $C_{16}H_{23}Li_2N_5O_{16}P_2,5H_2O$ requires N, 9·9; P, 8·7%). For ratio analysis solutions were used in which the guanosine contents were estimated spectroscopically [Found: guanosine : labile

phosphorus [4] : total phosphorus [4] : reducing hexose [5] (after hydrolysis at pH 2 for 15 min. at 100°) 1·02 : 0·86 : 2·00 : 0·95. Guanosine diphosphate glucose requires 1·00 : 1·00 : 2·00 : 1·00].

Guanosine Diphosphate Fructose.—Solutions of tri-n-octylammonium D-fructose 1-phosphate (32 mg., 0·052 mmole) and *NN'N''*-tricyclohexylguanidinium guanosine-5′ *N*-cyclohexylphosphoramidate (10 mg., 0·013 mmole) in anhydrous pyridine (5 ml. and 10 ml., respectively) were mixed and set aside at 28° for 4 days. Pyridine was removed by evaporation, water (10 ml.) was added, and the volume was reduced to 0·5 ml. by evaporation. Paper chromatography revealed the presence of D-fructose 1-phosphate, guanosine-5′ phosphate, and a compound, presumably guanosine diphosphate fructose, with the same R_F as guanosine diphosphate glucose. The reaction mixture was chromatographed as a band on Whatman No. 1 paper in the ethanol–ammonium acetate system. The band corresponding to guanosine diphosphate fructose was cut out and eluted with water. The hydrolysis experiments were carried out with this solution according to methods described previously.[1]

Paper Chromatography and Electrophoresis.—Nucleotides were examined on Whatman No. 1 paper in ethanol–1M-ammonium acetate (pH 3·8) (70 : 35 v/v) by descending development. The following $R_{adenosine}$ values were obtained: α-D-glucose 1-phosphate, 0·60; fructose 1-phosphate, 0·68; guanosine-5′ phosphate, 0·32; guanosine-5′ pyrophosphate, 0·05; diguanosine-5′ pyrophosphate, 0·27; guanosine-5′ *N*-cyclohexylphosphoramidate, 0·55; guanosine diphosphate glucose, 0·12; guanosine diphosphate fructose, 0·12; guanosine diphosphate mannose, 0·13.

Sugars were run on Whatman No. 1 paper in butanol–pyridine–water (6 : 4 : 3 v/v) by descending development. The following R_{ribose} values were obtained: glucose, 0·70; mannose, 0·83; fructose, 0·79. Sugars were also subjected to electrophoresis on Whatman No. 1 paper in 0·05M-sodium borate buffer (pH 9·2) when the following E_{ribose} values were obtained: glucose, 1·32; mannose, 0·94; fructose 1·17.

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[4] Fiske and Subbarow, *J. Biol. Chem.*, 1925, **66**, 375.
[5] Park and Johnson, *J. Biol. Chem.*, 1949, **181**, 149.

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497. *Arylation of 2-Furoic Acid in Meerwein's Diazo-reaction.*

By K. B. L. MATHUR and H. S. MEHRA.

p-NITRO- and *p*-CHLORO-BENZENEDIAZONIUM CHLORIDE have been reported [1] to give 5-aryl-2-furoic acids (I; R = aryl) on reaction with 2-furoic acid (I; R = H) in the presence of acetone, cupric chloride, and hydrochloric acid, but the details are lacking. We have reinvestigated this reaction at pH 3—5 (usual for arylation by the Meerwein's reaction [2]), because we thought that under the acid conditions (pH 1) stated to have been employed previously, other reactions with unsaturated acids, *e.g.*, decarboxylation, might not have been discernible.[3] But, as advocated [3a] earlier for reactions with water-soluble acids, the acetone so specifically recommended in other cases,[2] was omitted. Further the structures of the arylated acids have now been rigidly proved.

p-Chlorobenzenediazonium chloride and 2-furoic acid in the presence of cupric chloride and sodium acetate give an arylated acid in 20% yield. Using the method used by Hill *et al.*[4] for converting 5-methyl-2-furoic acid (I; R = Me) into 4-oxopent-2-enoic acid

[1] Malinowski, *Roczniki Chem.*, 1953, **27**, 54; *Chem. Abs.*, 1954, **48**, 13,678.
[2] (*a*) Meerwein, Buchner, and Emster, *J. prakt. Chem.*, 1939, **152**, 237; (*b*) Koelsch and Boekelheide, *J. Amer. Chem. Soc.*, 1944, **66**, 412.
[3] (*a*) Cf. Rai and Mathur, *J. Indian Chem. Soc.*, 1947, **24**, 383; (*b*) Denivelle and Razair, *Compt. rend.*, 1953, **237**, 570.
[4] Hill *et al.*, *Ber.*, 1890, **23**, 452; *Amer. Chem. J.*, 1893, **15**, 159; 1897, **19**, 650.

(II; R = Me), we oxidised the arylated acid by bromine water to *p*-chlorobenzoylacrylic acid (II; R = *p*-Cl·C_6H_4). The coupling product must therefore be 5-*p*-chlorophenyl-2-furoic acid (II; R = *p*-Cl·C_6H_4). There is indication that the initial product obtained by

the bromine oxidation is a mixture of *cis*- and *trans*-forms: the acid obtained by one crystallisation needs irradiation in presence of iodine in chloroform before it gives the melting point as recorded in the literature.

p-Bromo- and *m*- and *p*-nitro-benzenediazonium chlorides similarly gave monoarylfuroic acids that do not seem to be mixtures. The *m*-nitro-acid was also oxidised to *m*-nitrobenzoylacrylic acid, proving again that arylation occurred at the 5-position.

The experiments with *p*-chloro- and *p*-bromo-benzenediazonium chloride gave also, by decarboxylation, 2-*p*-chloro- and 2-*p*-bromo-phenylfuran but in yields of only a few percent. The amount of carbon dioxide evolved was, however, 10% and most of this clearly arose by decarboxylation of the unsubstituted furoic acid (cf. Bergmann *et al.*[5]).

The arylation of 2-furoic acid in the 5-position fits an aromatic character for this acid and corresponds to the homolytic arylation, mostly at the 2-position, undergone by furan itself.[6] The decarboxylation of the product, analogous to that of sorbic acid,[2b] shows the participation in the coupling reaction also of the diene form of the acid, though to a minute extent. Further, the homolytic arylation is here easier than that of benzoic acid

Experimental.—Coupling of p-*chlorobenzenediazonium chloride with* 2-*furoic acid.* *p*-Chloroaniline (6·36 g.) was dissolved in warm 25% hydrochloric acid (18 ml.). Ice (15—20 g.) was added and the precipitated hydrochloride diazotised with sodium nitrite (4 g.) in water (15 ml.). Separately, 2-furoic acid (5·6 g.) was dissolved in warm water (50 ml.) containing sodium acetate (16 g.); on cooling, the 2-furoic acid remained in solution. The diazotised solution was filtered through glass wool and added to the acid solution, followed by cupric chloride (2 g.) in water (10 ml.). There was brisk effervescence. The mixture was stirred for 3 hr. at 30° and then steam-distilled. The later part of the steam-distillate gave a small amount of 2-*p*-chlorophenylfuran,[6] m. p. 73°, dissolving in concentrated sulphuric acid with a permanganate colour. On cooling, the non-volatile material contained a red-brown solid (*ca.* 5 g.), which was filtered off, washed, and extracted with saturated sodium hydrogen carbonate solution (3 × 25 ml.). The combined extracts were acidified with hydrochloric acid, giving an acid precipitate that, after recrystallisation from 20% alcohol, had m. p. 194° (Found: C, 59·4; H, 3·7. Calc. for $C_{11}H_7O_3Cl$: C, 59·3; H, 3·15%). Recovery of this 5-*p*-chlorophenyl-2-furoic acid was easier with aqueous ammonia but then the product was slightly coloured. The yield of crude acid, m. p. 182—186°, was 2·2 g. (20%).

The acid product (0·6 g.) was dissolved in water (15—20 ml.) with the aid of alcohol. Bromine (0·9 g., 0·3 ml.) was added drop by drop with shaking to this solution. The residual bromine was also washed into the mixture with the aid of water (15 ml.). The mixture, with occasional shaking, was then kept at room temperature for 1 hr., then extracted with ether. The extract was dried (Na_2SO_4) and evaporated. The residue was semisolid and after crystallisation from benzene yielded crystals (0·2 g.), m. p. 147—148°.[7] These were dissolved in chloroform (10 ml.) containing traces of iodine and kept in sunlight for 12 hr. The chloroform was removed and the residue again crystallised from benzene, giving crystals, m. p. 156° alone or mixed with *p*-chlorobenzoylacrylic acid[7a] (Found: C, 56·5; H, 3·8. Calc. for $C_{10}H_7O_3Cl$: C, 57·0; H, 3·3%).

Coupling of other diazonium chlorides with 2-*furoic acid.* Diazotised *p*-bromoaniline (8·6 g.)

[5] Bergmann, Dimant, and Japhe, *J. Amer. Chem. Soc.*, 1948, **70**, 1618.
[6] Johnson, *J.*, 1946, 895.
[7] (*a*) Papa, Schwenk, Villani, and Klingsberg, *J. Amer. Chem. Soc.*, 1948, **70**, 3356; (*b*) Bogert and Ritter, *ibid.*, 1925, **47**, 532; (*c*) Freund, *J.*, 1952, 3068.

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was coupled with 2-furoic acid (5·6 g.) as described above. From the steam-distillate 2-*p*-bromophenylfuran, m. p. 84—86°, giving a permanganate colour in concentrated sulphuric acid,[6] was recovered. The sodium hydrogen carbonate extract of the residual solid provided the crude product (0·6 g.) which on crystallisation from 50% alcohol yielded 5-p-*bromophenyl-2-furoic acid*, m. p. 198° (Found: C, 49·1; H, 2·7. $C_{11}H_7BrO_3$ requires C, 49·4; H, 2·6%).

Coupling of diazotised *m*-nitroaniline (6·9 g.) in the same way gave 5-m-*nitrophenyl-2-furoic acid* (0·6 g., crude), m. p. 244° (from ethyl acetate) (Found: C, 56·5; H, 3·4. $C_{11}H_7NO_5$ requires C, 56·6; H, 3·0%). This acid with bromine water gave *m*-nitrobenzoylacrylic acid,[7b] m. p. and mixed m. p. 187°.

In the same way was obtained 5-*p*-nitrophenyl-2-furoic acid (from 50% alcohol), m. p. 246—247° (Found: C, 56·15; H, 2·7%). Freund[7c] obtained this acid by the oxidation of β-(5-*p*-nitrophenyl-2-furyl)acrylic acid and reported m. p. 204—205°.

Decarboxylation in the coupling reactions. The various diazotised bases (0·025 mole) were treated with 2-furoic acid (0·025 mole), and the evolved gases were swept in a current of carbon dioxide-free air into baryta water, giving barium carbonate (*ca.* 0·5 g., 10%). With the chloro-compound, the mixture was steam-distilled until 400 ml. had been collected. The distillate was extracted with ether (200 ml.) and the extract dried (Na_2SO_4). Evaporation at 30° *in vacuo* and then in a current of air gave 2-*p*-chlorophenylfuran (0·1 g., 2%). A sample of this furan (0·1 g.) when mixed with the chloro- and *p*-dichloro-benzene (0·3 g. each) was similarly recovered (0·09 g.) without much loss. This procedure was not quantitative for *p*-bromophenylfuran, but this was recovered (0·05 g.) by rejecting the first 25 ml. of the steam-distillate (supposed to contain mostly the Sandmeyer type of products) and extracting the rest of the distillate (400 ml.) with ether.

It was verified in separate experiments that the evolution of carbon dioxide was not due to spontaneous decarboxylation of the parent acid or the arylated acids, independently of the coupling process. Nor were the arylfurans the products of secondary process, *e.g.*, decomposition of the 5-arylated acids first formed.

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498. *Mixed Formals derived from Alcohols and Phenols.*

By Frank S. H. Head and (Miss) M. M. Williamson.

The reaction between phenols and formaldehyde in the presence of acid does not usually give rise to formals, since substitution in the aromatic nucleus and subsequent polymerisation occur more readily, but Breslauer and Pictet [1] obtained a mixed formal, methoxy-(phenoxy)methane, by treating phenol with aqueous formaldehyde (presumably containing methanol) and sulphuric acid at room temperature, and also from potassium phenoxide and chloromethyl methyl ether.

The following compounds have been made by the latter method: (2,4,6-tribromophenoxy)-, (2,4,5-trichlorophenoxy)-, and (2,3,4,5,6-pentachlorophenoxy)-methoxymethane, and ethoxy-(2,4,6-tribromophenoxy)methane. The two tribromophenoxy-compounds have also been obtained in about 15% yield by passing hydrogen chloride into a mixture of tribromophenol, paraformaldehyde, and the appropriate alcohol in chloroform.

Chloromethyl octadecyl ether treated with sodium methoxide gave octadecyloxymethoxymethane together with some dioctadecyloxymethane. The latter was also prepared from the chloromethyl ether and octadecanol, and directly from octadecanol and formaldehyde. An attempt to prepare di-(2,4,6-tribromophenoxy)methane by the

[1] Breslauer and Pictet, *Ber.*, 1907, **40**, 3784; see also Reychler, *Bull. Soc. chim. France*, 1907, (**4**), **1**, 1195.

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direct method failed. Chloromethyl octadecyl ether (m. p. 56·5—57·5°) and dioctadecyloxymethane (m. p. 58—59°) gave only a slight depression of melting point (1—2°) on admixture with octadecanol (59°). At one stage it was thought that these substances might be unchanged octadecanol, but infrared examination confirmed the absence of hydroxyl groups from the compounds.

Experimental

Infrared absorption spectra of the octadecanol derivatives were measured on films between rock-salt plates; spectra of the other compounds were measured as Nujol mulls. The spectra showed absence of hydroxyl and carbonyl groups.

(2,4,6-*Tribromophenoxy*)*methoxymethane*.—(*a*) A warm solution of sodium ethoxide [from sodium (2·3 g.) and ethyl alcohol (30 c.c.)] was added to a solution of 2,4,6-tribromophenol (33 g.) in dry ether (100 c.c.). Chloromethyl methyl ether (7·5 c.c.) was added to the cooled mixture. After a short time the mixture was poured into an excess of dilute sodium hydroxide, and the ether layer was washed with 1% sodium hydroxide, dried (K_2CO_3), and distilled. The residue (28·7 g.) consisted of (2,4,6-*tribromophenoxy*)*methoxymethane*, m. p. 65·5—66·5° (after repeated precipitation from acetone solution with an equal volume of water) (Found: C, 25·6; H, 2·0; Br, 62·7; O, 8·6; OMe, 8·3. $C_8H_7Br_3O_2$ requires C, 25·6; H, 1·9; Br, 64·0; O, 8·5; OMe, 8·3%).

(*b*) A stream of dry hydrogen chloride was passed for about 4 hr. into a mixture of 2,4,6-tribromophenol (82·7 g.), methanol (10 c.c.), and paraformaldehyde (7·5 g.) in washed and dried chloroform (500 c.c.) at room temperature. The paraformaldehyde slowly dissolved and an upper layer of liquid formed. The whole was poured into a solution of sodium hydroxide (30 g.) in water (500 c.c.), and the mixture cooled, and worked up as above. The formal (15 g.) had m. p. and mixed m. p. 65·5—66·5° after recrystallisation from aqueous acetone; the infrared spectra of the products from preparations (*a*) and (*b*) were almost identical.

Ethoxy-(2,4,6-*tribromophenoxy*)*methane*.—(*a*) By using method (*a*), but with chloromethyl ethyl ether (9·0 c.c.), *ethoxy*-(2,4,6-*tribromophenoxy*)*methane* was obtained as needles (25·5 g.), m. p. 57—58° raised to 59—60° by recrystallisation from a small amount of ethyl alcohol (Found: C, 27·7; H, 2·6; O, 8·3; OEt, 11·6. $C_9H_9Br_3O_2$ requires C, 27·8; H, 2·3; O, 8·2; OEt, 11·6%).

(*b*) Use of ethyl alcohol (14·4 c.c.) instead of methanol in method (*b*), above gave the formal (14 g.), m. p. and mixed m. p. 58·5—59·5° after recrystallisation from 67% aqueous acetone. The infrared spectra of the two samples were almost identical.

(2,4,5-*Trichlorophenoxy*)*methoxymethane*.—By method (*a*), 2,4,5-trichlorophenol (20 g.) gave a crude liquid (19·9 g.) which solidified at 0°. Recrystallisation from light petroleum (b. p. 60—80°) gave (2,4,5-*trichlorophenoxy*)*methoxymethane* (crystals), m. p. 53—55° (Found: C, 39·6; H, 2·9; OMe, 12·6. $C_8H_7Cl_3O_2$ requires C, 39·8; H, 2·9; OMe, 12·8%).

(2,3,4,5,6-*Pentachlorophenoxy*)*methoxymethane*.—Chloromethyl methyl ether (8·5 c.c.) was added to a suspension of technical sodium pentachlorophenoxide (32 g.) in dry ether (100 c.c.). The crude product (21·7 g.), worked up as above, was dissolved in acetone (150 c.c.), and the solution filtered and water (30 c.c.) added. (2,3,4,5,6-*Pentachlorophenoxy*)*methoxymethane* separated as needles (11·7 g.; m. p. 78—79°), which after further purification had m. p. 79—80° (Found: C, 31·1; H, 1·7; Cl, 56·8; O, 10·1; OMe, 9·8. $C_8H_3Cl_5O_2$ requires C, 31·0; H, 1·6; Cl, 57·1; O, 10·3; OMe, 10·0%).

Dioctadecyloxymethane.—(*a*) Chloromethyl octadecyl ether [2] (6·4 g.; m. p. 56·5—57·5° after crystallisation from ether) and a solution of octadecanol (5·4 g.) in pyridine (20 c.c.) were heated at 100° for 6 hr. The mixture was dissolved in chloroform, and the solution washed with dilute sodium carbonate and with water, dried (K_2CO_3), and evaporated, finally under reduced pressure. The residue (10·8 g.; m. p. 50—52°) was crystallised from ether and then from light petroleum (b. p. 60—80°), giving *dioctadecyloxymethane*, m. p. 58—59° [Found: C, 80·8; H, 14·0%; *M* (in camphor), 429. $C_{37}H_{74}O_2$ requires C, 80·4; H, 13·8%; *M*, 552].

(*b*) A mixture of octadecanol (27 g.), paraformaldehyde (3 g.), and concentrated sulphuric acid (1 c.c.) was heated at 100° for 6 hr. The product, worked up as above, had m. p. and mixed m. p. 58—59° (Found: C, 80·8; H, 13·7%; *M*, 408). The infrared spectra of materials prepared by methods (*a*) and (*b*) were almost identical.

[2] Kursanov and Setkina, *Zhur. priklad. Khim.*, 1943, **16**, 36.

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(Octadecyloxy)methoxymethane.—Chloromethyl octadecyl ether (85·6 g.) was added to the solution from sodium (9·2 g.) and methanol (200 c.c.), and the whole was refluxed for 2 hr., after which the methanol was distilled off. The residue was treated with water and extracted with chloroform; the extract was washed, dried (K_2CO_3), and evaporated. The crude product (70·5 g.) was crystallised from light petroleum (120 c.c.; b. p. 60—80°) and the crystals were discarded. The residue, recovered from the solvent, was crystallised from ethyl alcohol (35 c.c.), the crystals again being rejected and the solute (26 g.) recovered and dissolved in light petroleum (80 c.c.). The solution was left overnight in the refrigerator, freed from crystals, concentrated to half volume, and cooled to well below 0°. *(Octadecyloxy)methoxymethane* separated as waxy crystals (13 g.), m. p. 28—29°, very soluble in organic solvents, but insoluble in water (Found: C, 76·5; H, 13·5; OMe, 9·4. $C_{20}H_{42}O_2$ requires C, 76·4; H, 13·4; OMe, 9·9%).

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499. *The Pyrolysis of Divinylmercury and the Strength of the C–H Bond in Ethylene.*

By A. F. TROTMAN-DICKENSON and G. J. O. VERBEKE.

VALUES of 91·5 (ref. 1) and 122 (ref. 2) kcal. mole^{-1} for the strength of the C–H bond in ethylene, determined by electron impact, were reported several years ago. The present pyrolysis study was intended to narrow the range of choice. After the investigation began, Harrison and Lossing [3] determined the ionization potential of the vinyl radical directly and found $D(C_2H_3\text{–}H) = 105 \pm 3$ kcal. mole^{-1}, a value in better accord with the reactivity of methyl radicals with ethylene.[4]

Twenty-nine pyrolyses of divinylmercury were carried out by us in a typical toluene carrier flow system [5] between 502° and 642°. Most runs occupied 20 min., a few 10 or 30 min. First-order rate constants were calculated from the amount of mercury released. In eight runs below 590° concordant results were obtained from measurements of the ethylene, acetylene, and buta-1,3-diene formed. The range of conditions investigated was limited by the time available. In one run the pressure was 24 mm., for another 17 mm., and for the rest 16·1 mm. The contact times lay between 0·90 and 1·54 sec., except that in four runs where the reaction vessel was packed with fire-polished silica tubes the time rose to about 2·5 sec. In four runs near 601° the amount of divinylmercury passed in 20 min. varied between 346 and 3860 μmole without effect on the first-order rate constant; a fifth run with 423 μmole gave a 50% higher constant. Packing the reaction vessel did not alter the rate constants; hence if the rate is assumed to be independent of contact time, the initial decomposition of the alkylmercury is homogeneous.

The simplest reaction scheme that could be expected to account for the products is:

$$(C_2H_3)_2Hg \longrightarrow C_2H_3Hg^{\bullet} + C_2H_3^{\bullet} \quad \ldots\ldots\ldots (1)$$

$$C_2H_3Hg^{\bullet} \longrightarrow Hg + C_2H_3^{\bullet} \quad \ldots\ldots\ldots (2)$$

$$C_2H_3^{\bullet} + C_6H_5{\cdot}CH_3 \longrightarrow C_6H_5{\cdot}CH_2^{\bullet} + C_2H_4 \quad \ldots\ldots\ldots (3)$$

$$2C_2H_3^{\bullet} \longrightarrow C_4H_6 \quad \ldots\ldots\ldots (4)$$

$$2C_2H_3^{\bullet} \longrightarrow C_2H_4 + C_2H_2 \quad \ldots\ldots\ldots (5)$$

$$2C_6H_5{\cdot}CH_2^{\bullet} \longrightarrow (C_6H_5{\cdot}CH_2{\cdot})_2 \quad \ldots\ldots\ldots (6)$$

At the lower temperatures the rate constants, calculated from the gaseous products on the basis of this reaction mechanism, were essentially the same as those obtained, on

[1] Stevenson, *J. Amer. Chem. Soc.*, 1943, **65**, 209.
[2] Field, *J. Chem. Phys.*, 1953, **21**, 1506.
[3] Harrison and Lossing, *J. Amer. Chem. Soc.*, 1960, **82**, 519.
[4] Trotman-Dickenson and Steacie, *J. Chem. Phys.*, 1951, **19**, 169.
[5] Price and Trotman-Dickenson, *Trans. Faraday Soc.*, 1957, **53**, 939.

the assumption of first-order decomposition, from the amount of mercury set free. At higher temperatures the rate constants obtained from the gas analysis were lower than those based on the mercury determination. In one of the experiments at 696°, where complete decomposition of the alkylmercury was attempted, the gaseous products were collected. They corresponded to only 71% decomposition, whereas the mercury determination indicated 93·2%. Evidently an additional reaction becomes important at the higher temperatures. This is probably the condensation of vinyl radicals, or of acetylene, to less volatile material. The difference between k_{gas} and $k_{mercury}$ increases more rapidly with temperature in the packed reaction vessel, so the condensation is probably heterogeneous. An attempt was made to fit the relative reaction rates of vinyl radicals with one another and with toluene to an Arrhenius plot. Allowance was also made here for the occurrence of the reactions (7) and (8), which were presumed to be the source of small

$$C_2H_3^{\bullet} \longrightarrow C_2H_2 + H^{\bullet} \quad \ldots \quad (7)$$

$$H^{\bullet} + C_6H_5{\cdot}CH_3 \longrightarrow C_6H_5{\cdot}CH_2^{\bullet} + H_2 \quad \ldots \quad (8)$$

quantities of hydrogen found in the products, and the possible non-occurrence of reaction (5). None of these attempts fitted the results. The effect of an altered surface–volume ratio on the relative rates of production of C_2 and C_4 products showed that the combination of vinyl radicals is also partly heterogeneous.

An Arrhenius plot of the rate constants from the mercury determination, fitted by the method of least squares, yields

$$\log_{10} k\,(\text{sec.}^{-1}) = (11{\cdot}94 \pm 0{\cdot}2) - (48{,}300 \pm 900)/2{\cdot}303RT.$$

The errors, determined by the normal statistical method, may well be smaller than the systematic errors. The latter cannot be estimated with certainty. The rate constants, calculated from the mercury analysis, may reasonably be assumed to be the rate of dissociation of the first mercury–carbon bond in divinylmercury. If the activation energy for the back-reaction is zero, the measured activation energy corresponds to the strength of this bond. The heat of formation of divinylmercury is not known. However, if there is no interaction between the two double bonds and the value of D_2 in divinylmercury is the same as in dimethyl- and diethyl-mercury,[6] it can be said that:

$$D(CH_3{\cdot}Hg{-}CH_3) - D(C_2H_3{\cdot}Hg{-}C_2H_3) = 2D(CH_3{-}H) - 2D(C_2H_3{-}H).$$

Then $D(CH_3{-}H)$ may be taken as 103·9 kcal./mole (ref. 7) and $D(CH_3{\cdot}Hg{-}CH_3)$ as 51·3 kcal./mole (refs. 5 and 8). These values, together with the result of this study, give a value of 102·4 kcal./mole for the first hydrogen in ethylene and 63 kcal./mole for the heat of formation of the vinyl radical. Purely on a numerical basis, an uncertainty of 3 kcal./mole must be assigned to these values.

Experimental.—Divinylmercury was prepared from vinylmagnesium bromide and mercuric chloride in tetrahydrofuran.[9] The excess of Grignard reagent was destroyed with ammonium chloride solution, and the organic fraction dried (Na_2SO_4). After removal of the tetrahydrofuran, divinylmercury was distilled three times at *ca.* 20 mm. and stored under a vacuum at −183°.

Toluene was purified by partial pyrolysis and fractional distillation, and thoroughly degassed.

The pyrolysis apparatus [5] was modified to ensure that no extraneous mercury reached the reaction system. Mercury from the decomposition of the alkylmercury was removed from the gas stream by a U-trap immersed in an ice–salt bath. Bibenzyl was removed by carefully rinsing the trap with ether. The mercury was dissolved in nitric acid and converted into

[6] Gowenlock, Polanyi, and Warhurst, *Proc. Roy. Soc.*, 1953, *A*, **219**, 270.
[7] Fettis and Trotman-Dickenson, unpublished results.
[8] Gowenlock, Polanyi, and Warhurst, *Proc. Roy. Soc.*, 1953, *A*, **218**, 269.
[9] Bartocha, Brinkman, Kaesz, and Stone, *Proc. Chem. Soc.*, 1958, 116.

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mercuric nitrate with potassium thiocyanate.[10] The gaseous products of several experiments were collected. Ethylene, acetylene, and buta-1,3-diene were distilled from a LeRoy low-temperature still and measured in a gas-burette. The completeness of separation was checked by infrared analysis (Mr. J. L. Duncan is thanked for these analyses).

We are grateful for the award of an I.C.I. Fellowship to G. J. O. V. and to Dr. S. J. W. Price for preliminary experiments.

CHEMISTRY DEPARTMENT, EDINBURGH UNIVERSITY. [*Received, December 2nd,* 1960.]

[10] Kolthoff and Sandell, " Textbook of Quantitative Analysis," Macmillan, London, 1943, p. 116.

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500. *Solvent Shifts in the Infrared Spectra of Metal Carbonyls and Their Derivatives.*

By C. C. BARRACLOUGH, J. LEWIS, and R. S. NYHOLM.

RECENT work has shown that useful information can be obtained from the infrared spectrum of a compound in a variety of solvents.[1] The shifts are frequently much larger than previous theories, based on the variation in dielectric constant of the solvent, would suggest. This effect is most pronounced for compounds containing a group with a large dipole moment, *e.g.*, groups such as C=O, N=O, S=O. In the present work the infrared spectra of a variety of metal carbonyls and substituted metal carbonyls have been measured. The large solvent shifts observed in some cases suggest that appreciable solute-solvent interaction must be occurring in these cases, and the implications of these interactions are considered.

RESULTS

The spectra have been measured mostly in cyclohexane and chloroform, because of solubility limitations, and also because the bands become very broad and frequently overlap in the more polar solvents. The carbonyl stretching frequencies given in Tables 1—4 are grouped according to the nature of the compounds, and the frequencies are believed to be accurate to ± 2 cm.$^{-1}$.

TABLE 1. *Metal carbonyls; carbonyl frequencies in cm.*$^{-1}$.

$Fe(CO)_5$		$Mn_2(CO)_{10}$		$Co_2(CO)_8$		$Co_3(CO)_9$	
C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$
2021	2019	2043	2043	2068	2071	2029	1845
2000	1998	2013	2010	2058	2042	2022	
		1982	1980	2042	2005	1867	
						1857	

TABLE 2. *Substituted metal carbonyls; frequencies in cm.*$^{-1}$.

(D = *o*-phenylenebisdimethylarsine)

	Cr		Mo		W			
	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$		
$MD(CO)_4$...	2018	2012	2026	2024	2020	2016		
	1931	1922	1938	1934	1934	1923		
	1908	1898	1923	1918	1912	1905	$NiD(CO)_2$	
			1914	1894			C_6H_{12}	$CHCl_3$
$MD_2(CO)_2$	1866	1845	1887	1859		1850	2011	2001
	1815	1770	1828	1786		1774	1952	1934

TABLE 3. *Carbonyl halides; frequencies in cm.*$^{-1}$.

$Fe(CO)_4I_2$		$Fe(CO)_4Br_2$		$Mn(CO)_5I$	
C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$
2132	2136	2151	2156	2123	2123
2086	2091	2109	2114	2045	2043
2081	2071	2099	2109	2004	2006
2063		2075	2083		

[1] *Proc. Roy. Soc.*, 1960, **255**, 1—81.

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TABLE 4. *Carbonyl frequencies (in cm.$^{-1}$) for* $Ni(CO)_2(PPh_3)_2$.

Cyclohexane 2010, 1954; chloroform 2004, 1939; bromoform 1999, 1938; methylene iodide 1997, 1935

DISCUSSION

The unsubstituted metal carbonyls being considered first, one finds that there are no shifts for the frequencies corresponding to the terminal carbonyl groups except for cobalt carbonyl, although the bands become broader. It is noteworthy that the frequency corresponding to the bridging carbonyl groups in cobalt carbonyl undergoes a significant shift. The infrared spectrum for cobalt carbonyl in cyclohexane shows two bands for the bridging carbonyl groups but in chloroform all the bands are much broader and several overlap.

The shifts are most striking for the diarsine-substituted carbonyls and increase with the degree of substitution. For comparison the shifts for some organic carbonyl compounds are shown in Table 5 (taken from ref. 2), and it can be seen that the bisdiarsine-substituted carbonyls show even larger solvent shifts than these.

Dipole-moment measurements have been made on a number of substituted metal carbonyls,[3] including the two nickel compounds used in the present work, and values of the order of 3—5 Debyes were obtained. It was suggested that nearly all the dipole moment arose from the metal–substituent bond, and practically none from the carbonyl groups. The most obvious interpretation of the present results, however, is that a strong dipole must exist on the carbonyl group of the diarsine-substituted metal carbonyls and that the solvent shift is due to some form of interaction of this dipole with the solvent molecules. The nature of the interaction is uncertain; it is probably a dipole–dipole interaction of which several kinds are possible. In cobalt carbonyl the shift associated with the bridging carbonyl groups is in accord with the qualitative idea that these bridging groups are analogous to the carbonyl group in a cyclic ketone.

TABLE 5. *Carbonyl frequencies in cm.$^{-1}$.*

Solvent	Benzophenone	Cyclohexanone	Acetone
C_6H_{12}	1670	1724	1723
$CHCl_3$	1658	1705	1712

It is possible to interpret the increase in solvent shift from the mono- to the bis-diarsine derivatives of the Group VI metals in terms of the relative π bonding properties of arsenic ligands and carbon monoxide molecules. Present ideas on the structure of metal carbonyls[4] suggest there is appreciable double-bond character in the metal–carbon bonds due to back donation of electrons from the metal atom to the carbon monoxide groups through π bonds. It is believed that the arsenic and phosphorus atoms of the common ligands in substituted metal carbonyls do not possess such good electron-acceptor properties for this back donation.[5] The negative charge accumulated on the central metal atom still has to be dispersed in accordance with the Pauling electroneutrality principle, and it is assumed that the amount of back donation to the remaining carbonyl groups must be increased, leading to an increase in the metal–carbon bond order and a lowering in the carbon–oxygen bond order.

FIG. 1.

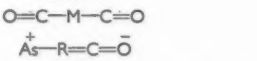
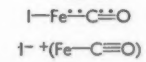


FIG. 2.



If this process is drawn up as shown in Fig. 1 it can be seen there is a build up of formal

[3] Bellamy and Williams, *Trans. Faraday Soc.*, 1959, **55**, 14.
[3] Chatt and Hart, *J.*, 1960, 1378.
[4] Sheline and Cable, *Chem. Rev.*, 1956, **56**, 1.
[5] Meriwether and Fiene, *J. Amer. Chem. Soc.*, 1959, **81**, 4200.

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negative charge on the oxygen atom of the carbonyl group, and this charge will increase as the metal–carbon bond order increases, *i.e.*, as more carbonyl groups are replaced.

The lowering of the carbonyl frequencies on substitution by phosphines and arsines has been observed previously but the present results on solvent shifts give additional support to current hypotheses concerning the relative π-bonding properties of carbon monoxide and tertiary phosphine and arsine ligands. The magnitude of the shift is greater the lower the original carbonyl frequency.

The iron carbonyl halides show quite different behaviour, the direction of the shifts being in the opposite direction to those already considered. Although the shifts are small, they are well outside the range of experimental error and again some form of solute–solvent interaction must be postulated. It is difficult to find an explanation in terms of a direct interaction of solvent molecules with the carbonyl groups since this type of mechanism will always produce a lowering in frequency towards more polar solvents.

A tentative explanation has been based on Bellamy's suggestion for a similar phenomenon with nitrosyl chloride [6] and is as follows. The iron–halogen bond is considered to have appreciable ionic character, *i.e.*, the wave function is regarded as involving a linear combination of the wave functions for the two structures shown in Fig. 2. In the ionic form the amount of back donation of negative charge from the metal to the carbonyl groups will be less than in the covalent structure because of the positive charge on the metal atom. This will mean that the carbon–oxygen bond order and hence the frequency will be higher in the ionic structure than in the covalent structure. When the iron carbonyl halide molecule is put in a polar solvent the ionic structure will be favoured, the ionic character of the metal halogen bond will increase and the carbonyl stretching frequencies will rise. An alternate way of looking at this problem is in terms of preferential solvation of the halide ion by the solvent.

The present results are relatively few in number, and the interpretations put forward are only tentative, but they do suggest another method of obtaining information about the structures of metal–carbonyl derivatives. From the purely practical viewpoint it appears that polar solvents such as chloroform are not satisfactory solvents for the measurement of solution spectra of metal carbonyl derivatives since the frequencies may be shifted by solute–solvent interaction. It is possible that the values of the frequencies observed for the solid state may be affected in a similar manner since inter- or intramolecular interactions may be taking place.

Experimental.—The spectra have been measured in a dilute solution of the various solvents, a Grubb-Parsons GS 2A double-beam grating spectrometer being used. Most of the compounds were prepared by published methods, but the authors are also grateful to Dr. M. Stiddard and Dr. D. V. R. Rao for supplies of some of these.

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[6] Bellamy, " The Infra-red Spectra of Complex Molecules," 2nd Edn., p. 382, Methuen & Co., Ltd., London, 1958.

501. *The Occurrence of Organotin Cations.*

By I. R. Beattie and T. Gilson.

Lower alkyltin chlorides, R_3SnCl and R_2SnCl_2, usually melt about 200° lower than the corresponding fluorides.[1] Furthermore, the chlorides are normally soluble in organic solvents whilst the fluorides are much less soluble and tend to dissolve only in hydroxylic solvents. This behaviour has led to the assumption [2] that organotin fluorides contain ions of the type R_2Sn^{2+} and R_3Sn^+. The trifluorides (like the triacetates) are unknown. The evidence for the discrete organotin cation in the solid is fragmentary. By analogy with the dimethylthallium ion,[3] isosteric with the mercury dialkyls, we might expect to find a linear dimethyltin ion. However, this entity would bear a double positive charge, making its free existence less likely.

On the basis of solubility data, Rochow *et al.*,[4] have stated: " We believe in anhydrous salts the Me_2Sn^{2+} ion resembles $:Sn^{2+}$." Although Me_2Tl^+ salts resemble $:Tl^+$ salts in solubility, it is difficult to accept solubility data *alone* as evidence of a particular formulation. The only other relevant data for the solid concerns the infrared spectra of certain organotin carboxylates. From the position of the C–O stretching frequencies, Okawara *et al.*[5] have suggested that these compounds contain carboxylate anions. However, the main problem here is a stereochemical one, not one of " degree of ionic character." For example, with the acetate group the symmetry is low, so that co-ordination would not be expected to alter the selection rules. Thus we should not expect to find great differences between the spectra of ionic acetates and chelate or bridging acetate groups. Alternatively, there would be considerable difference between the free carbonyl group in an ester and $\cdot CO_2$ acting as a chelate or bridging group. This is supported by some results by Duncanson *et al.*,[6] who have shown that carbonyl frequencies in tetra-acetyl diborate occur at 1718 and 1605 cm.$^{-1}$. These are interpreted in terms of two free carbonyl groups and two bridging or chelate carbonyl groups, respectively (since boron has a maximum covalency of four). The value of 1605 cm.$^{-1}$ for the bridging or chelate group is close to that found in ionic acetates, where the C–O stretching frequency of representation B_1 ν_8 has a value of about 1580 cm.$^{-1}$.

In order that the effect of bridging on the infrared spectra of acetates could be examined

C–O *stretching frequencies (in cm.*$^{-1}$*) of certain acetates.*

Representation * C_{2v}	NaOAc	Me_3SnOAc	$[Cu(OAc)_2,H_2O]_2$	$Be_4O(OAc)_6$	$Zn_4O(OAc)_6$	$(OAcMe_2Sn)_2O$
A_1 ν_3	1408	1428	1418	1481	1443	1410
B_1 ν_8	1578	1576	1603	1623	1598	1580

* Refers to NaOAc.

for compounds which would conventionally be regarded as covalent and where the crystal structures are known, we have observed the spectra of the basic acetates of zinc and beryllium [7] in solution in bromoform (to avoid crystal field effects). The Table shows

[1] For a recent review of organotin compounds see Ingham, Rosenberg, and Gilman, *Chem. Rev.*, 1960, **60**, 459.
[2] See, for example, Sidgwick, " Chemical Elements and Their Compounds," Oxford, 1950.
[3] Powell and Crowfoot, *Z. Krist.*, 1934, **87**, 370.
[4] Rochow, Seyferth, and Smith, *J. Amer. Chem. Soc.*, 1953, **75**, 3099.
[5] Okawara and Rochow, *J. Amer. Chem. Soc.*, 1960, **82**, 3285.
[6] Duncanson, Gerrard, Lappert, Pyszora, and Shafferman, *J.*, 1958, 3652.
[7] For the structures of basic zinc acetate and basic beryllium acetate, see Koyama and Saito, *Bull. Chem. Soc. Japan*, 1954, **27**, 112 (in English), and Wells, " Structural Inorganic Chemistry," Oxford, 1945.

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the C–O stretching vibrations for these compounds, together with those of certain organotin acetates,[8] sodium acetate,[9] and $[Cu(OAc)_2,H_2O]_2$.[10] Although the range of frequencies is quite large these spectra were taken under a variety of conditions. We found shifts of up to 50 cm.$^{-1}$ for $[Cu(OAc)_2,H_2O]_2$ depending on whether we studied a dilute potassium chloride disc or a mull in Nujol or hexachlorobutadiene. Further, the reported values of the frequency for sodium acetate cover a range of about 20 cm.$^{-1}$. Although the spectra of the organotin acetates do not show any similarity to that of acetoxytrimethylsilane,[8] with a carbonyl stretch at 1725 cm.$^{-1}$ and a C–O–(Si) stretch at 1267 cm.$^{-1}$, there is clearly no *simple* way of distinguishing between a discrete acetate ion and a bridging acetate group. Therefore the infrared spectra of organotin diacetates could be interpreted in terms of an octahedral distribution about the tin involving bridging or chelate acetate groups. In the case of trialkyltin acetates a co-ordination number of five appears to be necessary. This may at first appear to be unlikely. However, by analogy with iodine, which is in the same period as tin, and replacing the three equatorial lone pairs by alkyl groups, a formulation with two bridging acetate groups is acceptable. In a similar way we can rationalise the chemistry of the fluorides. Tin tetrafluoride is a solid which sublimes at 705° and is insoluble in most organic solvents, in sharp contrast to the other halides. This is not due to a sudden change in bond character between the fluoride and the chloride, but to a different crystal structure. The tin tetrahalides, other than the fluoride, almost certainly have molecular crystal structures.[11] Each tin in tin tetrafluoride appears from *X*-ray powder data to be surrounded by six fluorines (I), four bridging and two non-bridging.[12]

(I)

If the two non-bridging axial fluorines are replaced by alkyl groups we have a possible formulation for dialkyltin difluorides which would explain their anomalous properties.

The purpose of this Note is to draw attention to certain ambiguities in the interpretation of the infrared spectra of organotin carboxylates, and to indicate that an alternative interpretation is in agreement with the available data.

Experimental.—Basic beryllium acetate was prepared from beryllium carbonate and acetic acid.[13] Basic zinc acetate was prepared by *slow* sublimation from anhydrous zinc acetate at 200° in a high vacuum. The spectra were taken in bromoform (dried under calcium hydride), rock-salt optics being used.

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Department of Chemistry,
King's College, London, W.C.2. [*Received, December 14th*, 1960.]

[8] Okawara, Webster, and Rochow, *J. Amer. Chem. Soc.*, 1960, **82**, 3287.
[9] Jones and McLaren, *J. Chem. Phys.*, 1954, **22**, 1796; Nakamura, *J. Chem. Soc. Japan*, 1958, **79**, 1411; Ito and Bernstein, *Canad. J. Chem.*, 1956, **34**, 170.
[10] Nakamoto, Fujita, Tanaka, and Kobayashi, *J. Amer. Chem. Soc.*, 1957, **79**, 4904; for the structure of $[Cu(OAc)_2,H_2O]_2$ see van Niekerk and Schoening, *Acta Cryst.*, 1953, **6**, 227.
[11] See, for example, tin tetraiodide, Mellor and Fankuchen, *Acta Cryst.*, 1955, **8**, 343.
[12] Hoppe, *Angew. Chem.*, 1957, **69**, 399.
[13] T. Moeller, *Inorg. Synth.*, 1950, **3**, 4.

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502. *An Alkaloid from* Callichilia *Species.*

By M. D. Patel, J. M. Rowson, and D. A. H. Taylor.

Callichilia barteri (Apocyanaceae) is a small shrub, common in southern Nigeria. Extraction of the roots gave an alkaloid $C_{42}H_{48}N_4O_6$, having two basic centres, pK_B 9·5 and 7·4. Extraction of the less common *Callichilia stenosepala* gave the same alkaloid.

The properties of the alkaloid and its colour reactions are identical with those described for vobtusine, an alkaloid obtained by Goutarel, Rassat, Plat, and Poisson [1] from *Callichilia subsessilis* and from other plants.

Experimental.—Callichilia barteri. The ground roots (5 kg.) were percolated exhaustively with hot methylated spirit, and the extract concentrated to small volume. The residue was dissolved in chloroform and extracted with dilute sulphuric acid, the acid layer basified with ammonia, and the precipitate taken up in chloroform. Evaporation of the solvent gave a brown resin (30 g.) which was chromatographed on alumina. The material eluted with chloroform rapidly crystallised; recrystallisation from chloroform–methanol gave the alkaloid (4·3 g.) as brownish plates, m. p. 312° (decomp.), $[\alpha]_D^{20} = -320°$ ($CHCl_3$), readily soluble in chloroform and very sparingly in other solvents (Found: C, 71·8, 71·6; H, 6·9, 6·9; O, 13·4; N, 7·8; OMe, 9·3, 9·5%; equiv., 360. $C_{42}H_{48}N_4O_6$ requires C, 71·6; H, 6·9; O, 13·6; N, 7·95; 5OMe, 9·8%; equiv., 356). The alkaloid gave a blue colour with sulphuric acid containing ferric chloride, with nitric acid, and with nitrous acid. The *methiodide* formed yellowish crystals decomposing at 250° (Found: C, 50·1; H, 5·5; I, 24·1; N, 5·3. $C_{44}H_{54}I_2N_4O_6,4H_2O$ requires C, 49·8; H, 6·0; I, 24·0; N, 5·3%). Potentiometric titration of the base in hydrochloric acid indicated two basic centres, pK_B 9·5 and 7·4.

Callichilia stenosepala. The ground whole plant (2·7 kg.), collected in the forest near Benin, was extracted as above and gave the same alkaloid (0·7 g.), identical in spectra, m. p., and colour reactions.

Herbarium specimens are preserved in the Department of Pharmacy, Nigerian College, Ibadan.

Department of Pharmacy, Nigerian College, Ibadan.
Department of Chemistry, University College, Ibadan. [*Received, December 28th,* 1960.]

[1] Goutarel, Rassat, Plat, and Poisson, *Bull. Soc. chim. France,* 1959, 893.

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503. *The Synthesis and Reactions of Branched-chain Hydrocarbons. Part XIV.* The Free-radical Halogenation of t-Butylbenzene.*

By J. R. B. Boocock and W. J. Hickinbottom.

The free-radical halogenation of alkylbenzenes in the side chain is sufficiently well established to be a recognised test for a free-radical mechanism. In t-butylbenzene there is no α-CH group for this type of chlorination and it was of special interest to determine the products of free-radical halogenation.

Chlorination in the liquid phase by sulphuryl chloride promoted by benzoyl peroxide is reported by Kharasch and Brown [1] to give a 70% yield of ββ-dimethylphenethyl chloride. On the other hand, Backhurst, Hughes, and Ingold [2] reported, while our work was in

* Part XIII, Foster and Hickinbottom, *J.*, 1960, 680.

[1] Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 2147.
[2] Backhurst, Hughes, and Ingold, *J.*, 1959, 2742.

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progress, that t-butylbenzene undergoes rearrangement during chlorination in the gas phase under irradiation, giving αα-dimethylphenethyl chloride as the main product.

It is here shown that the free-radical chlorination of t-butylbenzene, in the liquid phase by *N*,2,4,6-tetrachloroacetanilide, gives a product containing about 75% of ββ-dimethylphenethyl chloride; also formed are 2-methyl-1-phenylpropene (~5%) and t-butylchlorobenzenes (~20%). In spite of a careful search, αα-dimethylphenethyl chloride was not identified among the products. The only possible evidence of rearrangement is the 2-methyl-phenylpropene which might conceivably arise by elimination of hydrogen chloride from the chlorinated product. If this is so the rearrangement does not amount to more than ~6%.

In the free-radical bromination of t-butylbenzene in the liquid phase by *N*-bromosuccinimide, nuclear bromination to give *p*-bromo-t-butylbenzene is the principal reaction; an unsaturated fraction boiling in the same range as 2-methyl-1-phenylpropene was obtained, but only as a minor constituent.

A significant feature of these halogenations is the occurrence of nuclear chlorination and bromination. There appears to be no previous record of substitution of this type in free-radical halogenation, although since this work was completed, Backhurst [3] has reported that vapour-phase bromination gives some nuclear-brominated product.

It is known, from other evidence, that the t-butyl group is chlorinated relatively slowly, and it is a reasonable assumption that there is a competing nuclear attack. Support for this is provided by free-radical bromination, which is known to be much slower [4] at a saturated system than chlorination, and consequently the main reaction is nuclear bromination.

Experimental.—Free-radical halogenation of t-butylbenzene. (*a*) Commercial t-butylbenzene, purified by distillation from sodium, had b. p. 167—168°, n_D^{20} 1·4927. The hydrocarbon (118 g.), *N*,2,4,6-tetrachloroacetanilide (55 g.), and benzoyl peroxide (2·2 g.) were stirred together at 90°. After 30 hr. there was no longer a positive reaction for the *N*-chloro-compound; 2,4,6-trichloroacetanilide separated on cooling, and more was precipitated by light petroleum (b. p. <40°). Distillation of the light petroleum solutions gave unchanged t-butylbenzene, b. p. 52—56°/14 mm., n_D^{20} 1·4919—1·4945, and a chlorinated product which was separated by distillation through a spinning-band column into the well-defined fractions: (*a*) b. p. 62—68°/10 mm., n_D^{20} 1·5308 (1·2 g.); (*b*) 86—87°/10 mm., n_D^{20} 1·5130 (4·6 g.); (*c*) b. p. 96—98°/11 mm., n_D^{20} 1·5245 (20 g.). Fraction (*a*) consisted mainly of 2-methyl-1-phenylpropene; it was unsaturated and was identified by its infrared spectrum. Fraction (*c*) was ββ-dimethylphenethyl chloride (Found: C, 71·0; H, 7·8; Cl, 20·9. Calc. for $C_{10}H_{13}Cl$: C, 71·2; H, 7·8; Cl, 21·0%). It gave a precipitate of silver chloride only slowly with boiling alcoholic silver nitrate. It was identified by comparison of its infrared spectrum with that of an authentic specimen prepared by Smith and Sellas's method [5] (b. p. 97·5/11 mm., n_D^{20} 1·5245). Both samples on nitration with fuming nitric acid gave the *p*-nitro-compound, m. p. 62—64°. Fraction (*b*) was essentially t-butylchlorobenzene (Found: C, 71·5; H, 7·9; Cl, 21·1. Calc. for $C_{10}H_{13}Cl$: C, 71·2; H, 7·8; Cl, 21·0%). Its infrared spectrum is identical with that of t-butylchlorobenzene obtained by chlorination of t-butylbenzene with chlorine and iron powder, and both samples gave 4-chloro-2-nitro-1-t-butylbenzene, m. p. 114·5—116°, on nitration.

(*b*) t-Butylbenzene (50 g.), *N*-bromosuccinimide (31 g.), and benzoyl peroxide were heated together at 90°. The reaction was stopped after 87 hr. although it had not finished. Distillation gave unchanged t-butylbenzene and fractions (*a*) (0·8 g.), b. p. 59—60°/10 mm., n_D^{20} 1·5038, olefinic and containing some labile bromine, (*b*) b. p. 92—94°/10 mm., n_D^{20} 1·5292 (0·8 g.), and (*c*) (8·7 g.) b. p. 100—103·5°/11 mm., $n_D^{17\cdot7}$ 1·5345—1·5343 (Found: C, 56·7; H, 6·0; Br, 37·2. Calc. for $C_{10}H_{13}Br$: C, 56·4; H, 6·15; Br, 37·5%). Fraction (*c*) was identified at *p*-bromo-t-butylbenzene by comparison of its infrared spectrum with that of an authentic

[3] Backhurst, *J.*, 1960, 1958.
[4] Walling, "Free Radicals in Solution," J. Wiley and Sons, Inc., New York, pp. 369—375.
[5] Smith and Sellas, *Org. Synth.*, 1952, **32**, 90.

XUM

specimen, by the preparation from it (Grignard) of *p*-t-butylbenzoic acid, m. p. and mixed m. p. 163·5—165·5°, and by nitration to give 4-bromo-2-nitro-1-t-butylbenzene, m. p. and mixed m. p. 133·5—134·5°.

For comparison, ββ-dimethylphenethyl bromide was prepared from the corresponding alcohol by the action of hydrogen bromide; it had b. p. 41°/0·1 mm., n_D^{20} 1·5401 (lit.,[6] b. p. 88—89°/5·3 mm., n_D^{25} 1·5382). This readily gave a precipitate of silver bromide with cold alcoholic silver nitrate; the product obtained from t-butylbenzene did not.

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[6] Duffin, Hughes, and Ingold, *J.*, 1959, 2740.

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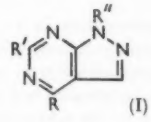
504. *The Preparation of Some* 1- *and* 2-β-D-*Ribofuranosylpyrazolo*[3,4-d]*pyrimidines.*

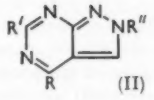
By J. DAVOLL and K. A. KERRIDGE.

A NUMBER of pyrazolo[3,4-*d*]pyrimidines, particularly the 4-amino- and 4-butylamino-compounds and their 1-methyl derivatives, have shown activity [1] *in vivo* against experimental neoplasms. The possibility that these compounds antagonise naturally occurring purines has been demonstrated by the partial reversal by adenine of the inhibition of *Neurospora crassa* by 4-aminopyrazolo[3,4-*d*]pyrimidine.[2] The ribosyl derivatives of some pyrazolo[3,4-*d*]pyrimidines were prepared because of the known greater effectiveness of some nucleosides than the corresponding free bases as antimetabolites.[3]

The pyrazolo[3,4-*d*]pyrimidines were prepared by Robins' methods,[4] except that 4,6-diaminopyrazolo[3,4-*d*]pyrimidine was more conveniently prepared by fusing guanidine carbonate with 3-amino-4-cyanopyrazole. Benzamido-derivatives were prepared by fusing the appropriate amino- or diamino-derivative with benzoic anhydride.

β-D-Ribofuranosylpyrazolo[3,4-*d*]pyrimidines were prepared by condensing the chloromercuri-derivatives of the appropriate pyrazolo[3,4-*d*]pyrimidines in toluene with tri-*O*-benzoyl-D-ribofuranosyl chloride. The resulting nucleoside benzoates were debenzoylated with either methanolic ammonia or sodium methoxide. The chloromercuri-derivatives of 4-benzamido- and 4,6-dibenzamido-pyrazolo[3,4-*d*]pyrimidine gave mixtures of


(I)


(II)

positional isomers of types (I) and (II), but only one isomer, of type (I), could be obtained from the condensation of the chloromercuri-derivative of the parent ring system with the ribosyl chloride.

Assignment of structure was made from a comparison of the ultraviolet absorption

[1] Skipper, Robins, Thomson, Cheng, Brockman, and Schabel, jun., *Cancer Research*, 1957, **17**, 579.
[2] Fuerst, Somers, and Hsu, *J. Bact.*, 1956, **72**, 387.
[3] Hall, *J. Amer. Chem. Soc.*, 1958, **80**, 1145, ref. 2.
[4] Robins, *J. Amer. Chem. Soc.*, 1956, **78**, 784.

spectra of the compounds obtained with the corresponding spectra of 4-amino-1- and -2-methylpyrazolo[3,4-*d*]pyrimidine [5,6] and 4,6-diamino-1-methylpyrazolo[3,4-*d*]pyrimidine.[7] The absorption maxima of all these compounds are shown in the Table.

The guanosine analogue (I; R = OH, R′ = NH_2, R″ = $C_5H_9O_4$) was prepared by standard methods [8] from the corresponding diamino-derivative, but attempts to prepare the isomeric compound (II) were unsuccessful.

Ultraviolet absorption spectra, $\lambda_{max.}$(mμ) ($10^{-3}\varepsilon$ *in parentheses*).

	In 0·1N-HCl	At pH 6·8	In 0·1N-NaOH
(I; R = R′ = H, R″ = Me) [5]	261	—	262
(I; R = R′ = H, R″ = $C_5H_9O_4$ [a])	—	261 (3·9)	—
(I; R = NH_2, R′ = H, R″ = Me) [5]	259 (9·4)	261 (9·0), 277 (9·25)	262 (9·7), 275 (9·7)
(I; R = NH_2, R′ = H, R″ = $C_5H_9O_4$ [a])	—	268 (11·4)	—
(I; R = R′ = NH_2, R″ = Me) [7]	—	—	276 (10·2)
(I; R = R′ = NH_2, R″ = $C_5H_9O_4$ [a])	—	258 (9·5), 276 (10·11)	—
(I; R = OH, R′ = NH_2, R″ = Me) [7]	—	—	267 (19·3)
(I; R = OH, R′ = NH_2, R″ = $C_5H_7O_4$ [a])	252 (14·45)	253 (14·55)	264 (11·0)
(II; R = NH_2, R′ = H, R″ = Me) [6]	268 (9·9)	270 [b] (8·7), 287 (11·0)	287 (10·9)
(II; R = NH_2, R′ = H, R″ = $C_5H_9O_4$ [a])	—	275 [b] (7·65), 284 (8·0)	—
(II; R = R′ = NH_2, R″ = $C_5H_9O_4$ [a])	—	263 (4·2), 290 (3·7)	—

[a] β-D-Ribofuranosyl. [b] Inflexion.

Experimental.—*4,6-Diaminopyrazolo*[3,4-*d*]*pyrimidine.* 3-Amino-4-cyanopyrazole [4] (10·8 g., 0·1 mole) was finely ground with guanidine carbonate (27·3 g., 0·3 equiv.), and the mixture heated at 150—160° for 40 min., then cooled and dissolved in boiling water (250 ml.), and the solution treated with charcoal. The material which separated was recrystallised from water (190 ml.) to give crystals (9·4 g.), m. p. 280—284°. A further recrystallisation from water gave pure 4,6-diaminopyrazolo[3,4-*d*]pyrimidine, m. p. 291°; $\lambda_{max.}$ at pH 11 254 (ε 7000), 274 (ε 8500); lit.,[9] $\lambda_{max.}$ at pH 11 255 (8100), 274 (ε 9400).

4-Benzamidopyrazolo[3,4-d]*pyrimidine.* 4-Aminopyrazolo[3,4-*d*]pyrimidine [4] (22 g., 0·2 mole) was heated with benzoic anhydride (68 g., 0·3 mole) at 180° for 45 min. The cooled, solidified product was ground with ether leaving a solid (36 g.) of indefinite m. p. This material was dissolved in 60% aqueous ethanol (1500 ml.), and the solution filtered and concentrated to 500 ml. by distillation at atmospheric pressure. The cooled slurry was centrifuged to give *4-benzamidopyrazolo*[3,4-d]*pyrimidine* (22 g.), m. p. 223—224° (Found: C, 59·4; H, 4·0; N, 28·5. $C_{12}H_9N_5O,\frac{1}{4}H_2O$ requires C, 59·1; H, 3·9; N, 28·7%).

4,6-Dibenzamidopyrazolo[3,4-d]*pyrimidine.* 4,6-Diaminopyrazolo[3,4-*d*]pyrimidine (30 g., 0·2 mole) was heated with benzoic anhydride (135·6 g., 0·6 mole) at 200° for 45 min. The cooled residue was recrystallised twice from butanol to give white needles of *4,6-dibenzamidopyrazolo*[3,4-d]*pyrimidine* (33 g.), m. p. 286° (Found: C, 63·5; H, 4·2; N, 23·1. $C_{19}H_{14}N_6O_2$ requires C, 63·7; H, 3·9; N, 23·5%).

Chloromercuri-derivatives. The pyrazolo[3,4-*d*]pyrimidine (0·1 mole) was added as a suspension in 50% aqueous ethanol (500 ml.) to a solution of mercuric chloride (0·1 mole) in the same solvent (150 ml.). To the stirred suspension was added N-sodium hydroxide (1 equiv.) at such a rate that the yellow colour of mercuric oxide disappeared before the next drop was added. Celite 545 (1 g. for 1 g. of base used) was then added to the white suspension which was stirred for an additional 30 min. The chloromercuri-derivatives were collected by filtration, washed with water, and dried. Yields were 80—90%.

*Reaction of chloromercuri-derivatives with tri-*O*-benzoyl-*D*-ribofuranosyl chloride.* The condensations and debenzoylations were carried out in the manner described by Kissman

[5] Cheng and Robins, *J. Org. Chem.*, 1956, **21**, 1240.
[6] Schmidt, Eichenberger, Wilhelm, and Druey, *Helv. Chim. Acta*, 1959, **42**, 763.
[7] Cheng and Robins, *J. Org. Chem.*, 1958, **23**, 852.
[8] Davoll and Lowy, *J. Amer. Chem. Soc.*, 1951, **73**, 1650.
[9] Robins, *J. Amer. Chem. Soc.*, 1957, **79**, 6407.

et al.[10] except that the ribosyl chloride was prepared with the addition of acetyl chloride,[11] and toluene instead of xylene was used as the solvent. The isomers were separated by crystallisation, the isomer of structure (I) being less soluble. Seed crystals were obtained by partition chromatography on Celite 545, water-saturated n-butanol being used as the mobile phase. Yields of mixed isomers were 10—20%. The following compounds were obtained by these methods:

1-β-D-*Ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = R′ = H, R″ = $C_5H_9O_4$), needles (from water), m. p. 216°, $[\alpha]_D^{23}$ −65·5° (*c* 0·98 in H_2O) (Found: C, 47·7; H, 4·9; N, 22·1. $C_{10}H_{12}N_4O_4$ requires C, 47·6; H, 4·8; N, 22·3%). 4-*Amino*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*-[3,4-d]*pyrimidine* (I; R = NH_2; R′ = H, R″ = $C_5H_9O_4$), needles (from water), m. p. 246°, $[\alpha]_D^{23}$ −23·1° (*c* 0·98 in H_2O) (Found: C, 45·1; H, 5·1; N, 26·2. $C_{10}H_{13}N_5O_4$ requires C, 44·9; H, 4·9; N, 26·2%). 4,6-*Diamino*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = R′ = NH_2, R″ = $C_5H_9O_4$), needles (from water), m. p. 253°, $[\alpha]_D^{23}$ −84·5° (*c* 0·49 in H_2O) (Found: C, 42·8; H, 5·4; N, 30·2. $C_{10}H_{14}N_6O_4$ requires C, 42·6; H, 5·0; N, 29·8%). 4-*Amino*-2-β-D-*ribofuranosyl*-2H-*pyrazolo*[3,4-d]*pyrimidine* (II; R = NH_2, R′ = H, R″ = $C_5H_9O_4$), needles (from water) m. p. 137° (decomp.), $[\alpha]_D^{21}$ −76·6° (*c* 0·39 in H_2O) (Found: C, 44·5; H, 5·2; N, 26·0. $C_{10}H_{13}N_5O_4$ requires C, 44·9; H, 4·9; N, 26·2%). 4,6-*Diamino*-2-β-D-*ribofuranosyl*-2H-*pyrazolo*[3,4-d]*pyrimidine* (II; R = R′ = NH_2, R″ = $C_5H_9O_4$), white microcrystals (from water), m. p. 230° (decomp.), $[\alpha]_D^{23}$ −55·5° (*c* 0·38 in H_2O) (Found: C, 40·1; H, 5·4; N, 27·5. $C_{10}H_{14}N_6O_4,H_2O$ requires C, 40·0; H, 5·3; N, 28·0%).

4,6-*Diacetamido*-1-*tri*-O-*acetyl*-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = R′ = AcNH, R″ = $C_{11}H_{15}O_7$). The 4,6-diamino-compound (0·56 g., 0·002 mole) was refluxed with acetic anhydride (5 ml.) for 45 min. A white crystalline solid (1·05 g., m. p. 110—128°) was obtained by distilling off the excess of acetic anhydride *in vacuo*. Recrystallisation of this material from alcohol (9 ml.) gave the *product* as needles (0·6 g.), m. p. 138—143° (decomp.) (Found: C, 48·4; H, 5·2; N, 17·3. $C_{20}H_{24}N_6O_9$ requires C, 48·8; H, 4·9; N, 17·1%). An identical product was obtained when the 4,6-diamino-compound (2·52 g.) was heated with acetic anhydride (27 ml.) and pyridine (50 ml.) on a steam-bath for 2 hr.

6-*Acetamido*-4-*amino*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = NH_2, R′ = AcNH, R″ = $C_5H_9O_4$). To the above penta-acetyl compound (0·5 g.) dissolved in methanol (8 ml.) was added a saturated solution of methanolic ammonia (16 ml.), and the mixture was kept for 24 hr. at 3°. Removal of solvent *in vacuo* and crystallisation of the residue from water (4 ml.) gave the *acetamido-compound* as white needles (0·27 g.), m. p. 122—126° (decomp.) (Found: C, 42·1; H, 5·8; N, 24·8. $C_{12}H_{16}N_6O_5,H_2O$ requires C, 42·1; H, 5·3; N, 24·6%).

6-*Acetamido*-4-*hydroxy*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = OH; R′ = AcNH; R″ = $C_5H_9O_4$). The above acetamido-compound (0·42 g.) suspended in a solution of sodium nitrite (1 g.) in water (5 ml.) was treated with 10% acetic acid (10 ml.), and the mixture kept for 24 hr. at room temperature. The nucleoside slowly dissolved. This solution was evaporated *in vacuo*, treated with ethanol (10 ml.), and concentrated to 4 ml., slowly giving a white solid (0·25 g.). Crystallisation from water gave the *hydroxy-compound* (0·2 g.) as needles, m. p. 235° (Found: C, 44·5; H, 5·0; N, 21·1. $C_{12}H_{15}N_5O_6$ requires C, 44·3; H, 4·7; N, 21·5%).

6-*Amino*-4-*hydroxy*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = OH; R′ = NH_2; R″ = $C_5H_9O_4$). The above compound (0·4 g.) was refluxed with 0·3N-sodium methoxide (8 ml.) for 0·5 hr. The solution was neutralised with 10% aqueous acetic acid and evaporated to dryness *in vacuo*. Crystallisation of the residue from water (9·5 ml.) gave needles (0·3 g.), m. p. 263° (Found: C, 42·2; N, 4·9; N, 24·4. $C_{10}H_{13}N_5O_5$ requires C, 42·4; H, 4·6; N, 24·7%).

The authors thank Dr. R. E. Bowman for many helpful discussions, Miss E. M. Tanner for determination of the spectra, and Mr. F. Oliver for the microanalyses.

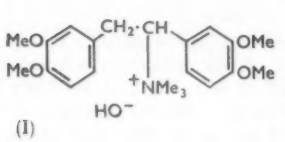
PARKE, DAVIS & COMPANY, RESEARCH DEPARTMENT,
STAINES ROAD, HOUNSLOW, MIDDLESEX. [*Received, January 18th*, 1961.]

[10] Kissman, Pidacks, and Baker, *J. Amer. Chem. Soc.*, 1955, **77**, 18.
[11] Baker and Schaub, *J. Amer. Chem. Soc.*, 1955, **77**, 5900.

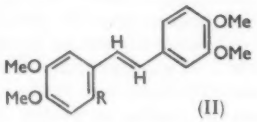
505. cis- *and* trans-3,3′,4,4′-*Tetramethoxystilbenes.*

By A. R. Battersby and I. A. Greenock.

The Hofmann elimination reaction is known to be concerted and bimolecular.[1,2] Of the two transition states which allow *trans*-coplanar elimination [1,3] from the methohydroxide (I), that which leads to the *trans*-3,3′,4,4′-tetramethoxystilbene (II; R = H) should be greatly favoured by non-bonded interactions.[4] It was therefore surprising when the stilbene prepared [5] by this reaction showed an ultraviolet absorption curve closely corresponding with those of known *cis*-stilbenes.[6] Our interest in this anomaly was increased by the report of another stilbene, apparently *cis*, prepared by an elimination reaction.[7] The tetramethoxystilbene had the m. p. reported [8] for 3,3′,4,4′-tetramethoxystilbene, but in none of these studies was the stereochemistry established. Accordingly, *cis*- and *trans*-3,3′,4,4′-tetramethoxystilbenes (II and III; R = H) were prepared.



(I)



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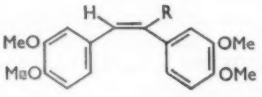


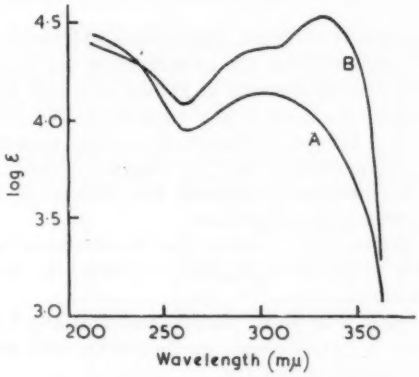
(III)

It is firmly established [9] that *trans*-cinnamic acids are formed in the Perkin reaction so that the acid obtained [10] by condensation of veratraldehyde with 3,4-dimethoxyphenylacetic acid has the structure (III; R = CO_2H). Stereospecific decarboxylation [11] of this acid over copper chromite in quinoline yielded *cis*-3,3′,4,4′-tetramethoxystilbene (III; R = H), m. p. 117—118° (ultraviolet absorption, curve A), which differed from the product of the Hofmann elimination. Catalytic hydrogenation of the *cis*-stilbene (III; R = H) yielded the known 3,3′,4,4′-tetramethoxybibenzyl.

Isomerisation of the *cis*-stilbene by iodine in boiling nitrobenzene [11] gave the *trans*-stilbene (II; R = H), m. p. 153—154°, which was identical with the Hofmann product. When the ultraviolet absorption of samples of stilbene from the isomerisation route and from the Hofmann elimination were measured without delay they showed the same curve which is typical of *trans*-stilbenes (curve B). The same result was obtained when a freshly prepared solution was kept in the dark for 38 days before measurement of the absorption. However, when the solution was kept on the bench (no direct sunlight), the absorption spectrum changed; after 10 days the curve was that of the *cis*-stilbene.

[1] Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093, and refs. therein.
[2] *Inter al.*, Hückel, Tappe, and Legutke, *Annalen*, 1940, **543**, 191; von Doering and Meislich, *J. Amer. Chem. Soc.*, 1952, **74**, 2099; Shiner and Smith, *J. Amer. Chem. Soc.*, 1958, **80**, 4995.
[3] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066; Booth and King, *J.*, 1958, 2688, and earlier papers; Jewers and McKenna, *J.*, 1960, 1575, and earlier papers.
[4] Cram, Greene, and DePuy, *J. Amer. Chem. Soc.*, 1956, **78**, 790; Barton and Cookson, *Quart. Rev.*, 1956, **10**, 48, and refs. therein.
[5] Battersby and Binks, *J.*, 1958, 4333.
[6] Calvin and Alter, *J. Chem. Phys.*, 1951, **19**, 765.
[7] Bergmann and Pelchowicz, *J. Amer. Chem. Soc.*, 1953, **75**, 4281.
[8] Feuerstein, *Ber.*, 1901, **34**, 415; Richtzenhain and von Hofe, *Ber.*, 1939, **72**, 1890; Wood, Bacon, Meibohm, Throckmorton, and Turner, *J. Amer. Chem. Soc.*, 1941, **63**, 1334; Quelet, Hoch, Borgel, Mansouri, Pineau, Tchiroukine, and Vinot, *Bull. Soc. chim. France*, 1956, 26.
[9] Collected refs. given by Zimmerman and Ahramjian, *J. Amer. Chem. Soc.*, 1959, **81**, 2086.
[10] Walker, *J. Amer. Chem. Soc.*, 1954, **76**, 3999.
[11] Taylor and Crawford, *J.*, 1934, 1130; Ruggli and Staub, *Helv. Chim. Acta*, 1937, **20**, 37.

The Hofmann product is thus the expected *trans*-stilbene (II; R = H) and the ultraviolet absorption recorded [5] is that of a *cis*-stilbene as a result of very ready photochemical isomerisation,[12] no doubt due to direct sunlight. The stilbene (II; R = CH_2·NMe_2), also



prepared [5] by Hofmann elimination, shows a typical *trans*-stilbene absorption spectrum which changes under the influence of light to that of a *cis*-stilbene.

Experimental.—cis-3,3′,4,4′-*Tetramethoxystilbene* (III; R = H). α-(3,4-Dimethoxyphenyl)-3,4-dimethoxycinnamic acid [10] (3·03 g.) was added during 5 min. to a suspension of copper chromite (0·38 g.) in quinoline (12 ml.) at 210°. The temperature was then raised to 220° for 25 min. and the cooled mixture was treated with an excess of 4N-hydrochloric acid (100 ml.). An oil separated which was extracted into ether, and the extracts were washed with dilute acid, aqueous sodium carbonate, and water. Evaporation of the dried ethereal solution and recrystallisation of the residue from ethanol yielded cis-3,3′,4,4′-*tetramethoxystilbene* (III; R = H) (2·0 g.), m. p. 117—118° (Found: C, 71·6; H, 6·7; OMe, 41·7. $C_{18}H_{20}O_4$ requires C, 72·05; H, 6·7; OMe, 41·3%); $\lambda_{min.}$ 263, $\lambda_{max.}$ 302 mμ (log ε 3·93 and 4·13, respectively) in ethanol. There were only very weak bands at 930 and 975 $cm.^{-1}$.

Hydrogenation of the foregoing product in ethanol at 23°/755 mm. over platinum (uptake 1·04 mol.) yielded 3,3′,4,4′-tetramethoxybibenzyl, m. p. and mixed m. p. 108—109°, having an infrared spectrum identical with that of an authentic sample.

trans-3,3′,4,4′-*Tetramethoxystilbene* (II; R = H). A solution of the above stilbene (5 g.) and iodine (0·1 g.) in anhydrous nitrobenzene (5 ml.) was heated under reflux for 15 min. The crystals which separated from the cooled solution were collected and recrystallised from ethanol to give the *trans*-stilbene (II; R = H) (3·72 g.), m. p. and mixed m. p. with sample from Hofmann elimination,[5] 153—154° (Found: C, 72·2; H, 6·5. Calc. for $C_{18}H_{20}O_4$: C, 72·05; H, 6·7%); $\lambda_{min.}$ 261, $\lambda_{max.}$ 330 mμ (log ε 4·09 and 4·54, respectively) in ethanol. The infrared spectra of the two samples of *trans*-stilbene were identical (strong band at 960 $cm.^{-1}$, CH out-of-plane deformation).

THE UNIVERSITY, BRISTOL.

[*Received, January 18th*, 1961.]

[12] Stoermer, *Ber.*, 1909, **42**, 4871.

506. *The Structure of Disalicylaldehydenickel.*

By J. R. Miller and A. G. Sharpe.

Curtiss, Lyle, and Lingafelter [1] found disalicylaldehydenickel to be isomorphous with its zinc analogue; they suggested that the co-ordination was tetrahedral on the grounds that all tetraco-ordinated zinc compounds of known structure were tetrahedral, and for several years the compound occupied a key position in the stereochemistry of nickel. However, Lyle, Morosin, and Lingafelter [2] have since found that the unit cell of the nickel compound is large and unsymmetrical, and, by comparison with bisacetylacetonenickel,[3] have suggested that it is polymeric, containing four trimers in the unit cell. We here report evidence which confirms this suggestion.

The compound was prepared by heating the dihydrate *in vacuo* at 100° for 80 hr. (Found: C, 54·0; Ni, 19·6. Calc. for $C_{14}H_{10}NiO_4$: C, 55·9; Ni, 19·5%); it was amorphous and could not be recrystallised.

The magnetic moment is 3·28 B.M. (Basolo and Matoush [4] found 3·0 B.M.). This almost certainly rules out a square-planar configuration, and indicates distorted tetrahedral, octahedral, or tetragonal symmetry.

In the visible region, the reflectance spectrum is almost identical with that of bisacetylacetonenickel, but rather different from that of a solution of nickel chloride and salicylaldehyde in dimethylformamide, which was taken by Maki [5] as a spectrum of the anhydrous compound. The important spectra are shown in the Table. Absorption maxima are in wavenumbers.

$Ni(SA)_2$	8850	*ca.* 13,700 (40%)	15,270	25,000 (100%)
Reflectance	(54% abs.)	infl.	(47%)	charge-transfer
$Ni(acac)_2$ [6]	8800	12,900	15,250	—
In benzene	($\varepsilon = 12$)	infl. ($\varepsilon = 5$)	($\varepsilon = 12$)	—
$NiCl_2$ + SAH [5]	7810	12,990 (0·12)	16,000 (0·16)	—
In DMF	(o.d. 0·14)	14,290 (0·16)	17,240 (0·14)	
$Ni(SA)_2,2H_2O$ [5]	9350 (0·26)	12,990 (0·07)	15,870 (0·36)	23,810 (0·80)
Reflectance	10,530 (0·15)			

SAH = Salicylaldehyde; acacH = acetylacetone; DMF = dimethylformamide.

These spectra are quite different from those of known tetrahedral nickel(II) complexes,[7] and this configuration is therefore not further discussed. Jørgensen [6] interpreted the acetylacetonate spectrum on the basis of an octahedral configuration with tetragonal splitting, whilst Maki [5] preferred a planar configuration with axial perturbation; the difference is only one of degree.

There are two possible ways by which the nickel atom could have an approximately octahedral environment: the benzene rings of one molecule could co-ordinate to the nickel atoms of adjacent molecules, or the oxygen atoms of adjacent molecules could be shared between nickel atoms. The first possibility is considered unlikely because the infrared spectrum of the anhydrous compound is very similar to that of the dihydrate, the

[1] Curtiss, Lyle, and Lingafelter, *Acta Cryst.*, 1952, **5**, 388.
[2] Lyle, Morosin, and Lingafelter, *Acta Cryst.*, 1959, **12**, 938.
[3] Bullen, *Nature*, 1956, **177**, 537.
[4] Basolo and Matoush, *J. Amer. Chem. Soc.*, 1953, **75**, 5663.
[5] Maki, *J. Chem. Phys.*, 1958, **29**, 162.
[6] Jørgensen, *Acta Chem. Scand.*, 1955, **9**, 1362.
[7] See, for example, Gruen and McBeth, *J. Phys. Chem.*, 1959, **63**, 393.

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crystal structure of which precludes interaction between the nickel atoms and the benzene rings.[8] The conclusion is that the substance has a polymerised structure, individual formula units being linked through oxygen atoms.

Fackler and Cotton [9] have recently found that complexes of nickel(II) with certain β-diketones are associated in solution, and that their anomalous magnetic moments may be explained in terms of equilibria: monomer (red, diamagnetic) $\rightleftharpoons$ associated species (green, paramagnetic). We suggest that the similarity of the spectra of anhydrous bisacetylacetonenickel in benzene solution and of the solid dihydrate [5,6] must be due to a similar phenomenon, and that such association may be of general occurrence.

We thank Dr. A. R. Caverhill, of Imperial Chemical Industries Limited, Fibres Division, Harrogate, for the reflectance spectrum of disalicylaldehydenickel, and the D.S.I.R. for a maintenance grant (to J. R. M.).

UNIVERSITY CHEMICAL LABORATORY,
CAMBRIDGE. [*Received, December 21st,* 1960.]

[8] Lingafelter, Breazeale, and Stewart, *Acta Cryst.*, 1957, **10**, 785.
[9] Fackler and Cotton, *J. Amer. Chem. Soc.*, 1960, **82**, 5005.

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507. 6-*Methylthiamine Chloride Hydrochloride.*

By J. BIGGS and P. SYKES.

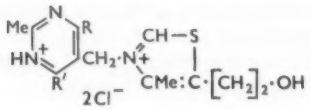
IT has been suggested [1] that thiamine chloride hydrochloride, when acting as a catalyst in the non-enzymic decarboxylation of pyruvate in the presence of acetaldehyde to yield acetoin + carbon dioxide,[2] first assumes a conformation in which the unsubstituted 6-position of the pyrimidine nucleus is spatially adjacent to the 2′-position of the thiazole nucleus (I; R = H, R′ = NH_2). The attack by pyruvate on this position in the thiazole (the vital stage in the above decarboxylation) [3] would then be sterically facilitated, whereas the pyrimidine 4-amino-group which is in close proximity in the conformation usually written for thiamine (I; R = NH_2, R′ = H) could well inhibit the pyruvate's close approach. We have, therefore, as a test of the hypothesis, synthesised 6-methylthiamine chloride hydrochloride (I; R = Me, R′ = NH_2) in which the steric advantage of the former conformation has been extinguished and which would thus be expected on the above hypothesis to exhibit little or no catalytic activity.

4-Amino-5-cyano-2,6-dimethylpyrimidine (II; R = CN), prepared by a slight modification of the method of Todd and his co-workers,[4] was reduced catalytically to yield 4-amino-5-aminomethyl-2,6-dimethylpyrimidine (II; R = $CH_2{\cdot}NH_2$). Treatment of this diamine with carbon disulphide, alkali, and 5-acetoxy-3-chloropentan-2-one yielded the thiazoline-2-thione (III), which on oxidation with hydrogen peroxide followed by exchange of SO_4^{2-} by $2Cl^-$ yielded the vitamin analogue (I; R = Me, R′ = NH_2) in the usual way.[5]

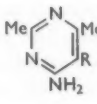
The addition of alkali to its aqueous solution produced a yellow colour which was changed into a thiochrome-like fluorescence on oxidation with ferricyanide—observations in accord with our views on the action of oxidising agents on thiamine itself.[6] 6-Methylthiamine (I; R = Me, R′ = NH_2) was found, like thiamine, to undergo ready exchange

[1] Private communication from Professor Eberhardt.
[2] Mizuhara, Tamura, and Arata, *Proc. Japan Acad.*, 1951, **27**, 302; Downes and Sykes, *Chem. and Ind.*, 1957, 1095.
[3] Breslow, *J. Amer. Chem. Soc.*, 1958, **80**, 3719.
[4] Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 388.
[5] Biggs and Sykes, *J.*, 1959, 1849.
[6] Sykes and Todd, *J.*, 1951, 534; Nesbitt and Sykes, *J.*, 1954, 4585.

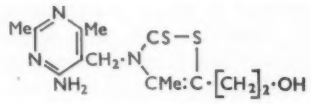
in deuterium oxide of the hydrogen atom in the 2′-position of the thiazole nucleus [7] and on being tested as a catalyst in the non-enzymic conversion of pyruvate + acetaldehyde ⟶ acetoin + carbon dioxide it showed 18% of the activity exhibited by thiamine under similar conditions. The magnitude of this catalytic activity, compared with that (5%)



(I)



(II)



(III)

of the isomer in which a methyl group has been introduced on the nearby internuclear methylene group but which still contains an unsubstituted pyrimidine 6-position,[5] suggests that the above hypothesis is untenable.

Experimental.—*4-Amino-5-cyano-2,6-dimethylpyrimidine* (II; R = CN). The method of Todd and his co-workers [4] was essentially followed but use of two mol. of acetamidine per mol. of malononitrile, instead of one, raised the yield from 50 to 90%. The product had m. p. 227° (decomp.) [lit.[4] m. p. 218°, and Huber and Hölscher [8] (using a different method), m. p. 220·5°] (Found: C, 57·1; H, 5·5; N, 38·2. Calc. for $C_7H_8N_4$: C, 56·9; H, 5·4; N, 37·8%).

4-Amino-5-aminomethyl-2,6-dimethylpyrimidine (II; R = $CH_2{\cdot}NH_2$). Catalytic reduction of the above cyanopyrimidine in glacial acetic acid–3N-hydrochloric acid with palladium–charcoal (10%) as catalyst yielded the dihydrochloride (cf. Huber and Hölscher [8]), m. p. 297—298° (decomp.) [lit.[8] m. p. 192—193° (decomp.) (? misprint)]. When an aqueous solution of the dihydrochloride was made alkaline with sodium hydrogen carbonate, solid separated which on recrystallisation from water yielded the *diamine* as needles, m. p. 200° (Found: C, 55·0; H, 8·2; N, 37·1. $C_7H_{12}N_4$ requires C, 55·2; H, 8·0; N, 36·8%).

3-(4-Amino-2,6-dimethyl-5-pyrimidylmethyl)-5-2′-hydroxyethyl-4-methylthiazoline-2-thione (III). The above diamine dihydrochloride (2·1 g.) was dissolved in water (8 ml.) and sodium hydroxide (0·75 g., 2 mol.) added, followed by ethanol (6 ml.), ammonia (*d* 0·88; 0·78 g.) and carbon disulphide (0·88 g.). The mixture, which became warm, was shaken until all the carbon disulphide had dissolved. 5-Acetoxy-3-chloropentan-2-one (1·65 g.) was added, the mixture was shaken vigorously for 30 min. and set aside overnight. The residue obtained on evaporating the mixture to dryness under reduced pressure was dissolved in 3N-hydrochloric acid (10 ml.), and the resulting solution warmed at 60° for 15 min. and then made just alkaline with sodium hydrogen carbonate. Solid separated which on recrystallisation from methanol (charcoal) yielded the *thiazoline-2-thione* (2·07 g., 71%) as needles, m. p. 246° (Found: C, 50·5; H, 6·0; N, 18·2. $C_{13}H_{18}N_4OS_2$ requires C, 50·3; H, 5·8; N, 18·1%).

3-(4-Amino-2,6-dimethyl-5-pyrimidylmethyl)-5-2′-hydroxyethyl-4-methylthiazolium chloride hydrochloride (*6-methylthiamine chloride hydrochloride*) (I; R = Me, R′ = NH_2). The thiazoline-2-thione (1·0 g.), water (30 ml.), and 24% hydrogen peroxide solution (1·33 g., 3 mol.) were stirred until the solid had dissolved (4 hr.), then treated with barium chloride solution until solid was no longer precipitated. The barium sulphate was removed on a centrifuge, and the solution evaporated to dryness. The residue was dissolved in methanol (20 ml.), decolorised with charcoal, and ether (30 ml.) then added slowly during 2 hr. The quaternary *chloride hydrochloride* (0·61 g., 54%) separated as needles, m. p. 233° (decomp.) (Found: C, 40·4; H, 6·4; N, 14·5. $C_{13}H_{20}Cl_2N_4OS,2H_2O$ requires C, 40·4; H, 6·2; N, 14·5%).

Exchange in deuterium oxide solution; nuclear magnetic resonance spectra. The above chloride hydrochloride (0·25 g.) was dissolved in water (0·25 ml.) and treated with N-sodium hydroxide (0·70 ml., 1 mol.); the solution exhibited a sharp peak on the hydrogen nuclear magnetic resonance spectrum at 181 cycles/sec. to the lower field side of the resonance of the hydrogen nuclei in the solvent water, corresponding to the 2-hydrogen atom in the thiazole nucleus.[5,7] A second portion of the chloride hydrochloride was then similarly converted into

[7] Breslow, *J. Amer. Chem. Soc.*, 1957, **79**, 1762.
[8] Huber and Hölscher, *Ber.*, 1938, **71***B*, 87.

the quaternary chloride, the solution freeze-dried, the residue dissolved rapidly in deuterium oxide, and the spectrum immediately examined: the peak at 181 cycles/sec. was no longer detectable.

Catalytic activity in the acetoin test. The test [2] was run in triplicate and the acetoin produced was estimated.[9] The above analogue exhibited 18% of the catalytic activity of the thiamine chloride hydrochloride, used as a control.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 24th*, 1961.]

[9] Westerfeld, *J. biol. Chem.*, 1945, **161**, 495.

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508. *Preparation and Properties of Trifluoromethylthiosilver.*

By H. J. EMELÉUS and D. E. MACDUFFIE.

TRIFLUOROMETHYLTHIOSILVER was prepared by Man, Coffman, and Muetterties [1] by reaction of aqueous silver nitrate with bistrifluoromethylthiomercury; the latter being prepared by heating mercuric fluoride with carbon disulphide. This Note describes the direct preparation of the silver compound in 70—80% yield from silver fluoride and carbon disulphide in an autoclave at 140°:

$$3AgF + CS_2 = AgS{\cdot}CF_3 + Ag_2S$$

The compound, isolated by extraction with acetone, was a white solid which was stable in air but decomposed when heated above 80° in a glass vessel *in vacuo*. Its infrared spectrum showed strong absorption bands at 1138, 1103, and 1083 cm.$^{-1}$ (C–F stretching), a sharp band of medium intensity at 755 cm.$^{-1}$ (C–S stretching, CF_3 deformation), and a number of weaker bands at 1200—1500 and 400—800 cm.$^{-1}$. The chief frequencies are also found in the spectrum of the mercurial.[2]

The compound was insoluble in water, dilute or concentrated hydrochloric acid, and dilute nitric acid but dissolved in hot 1 : 1 nitric acid. It dissolved readily in acetone, acetonitrile, dimethyl sulphoxide, and *NN*-dimethylformamide. The solubility in other solvents (in mg. per 100 g. of solvent at 24°) was: ether, 15·0; toluene, 13·5; hexane, 6·7; benzene, 5·1; carbon disulphide, 4·8; carbon tetrachloride, 0·2. It also dissolved in pyridine but a 10^{-2}M solution deposited a black precipitate after a few days at 20°. When the solvent was removed at 0° from a fresh pyridine solution, the adduct $2AgS{\cdot}CF_3,C_5H_5N$ remained. Dimethylamine gave the adduct $2AgS{\cdot}CF_3,Me_2NH$.

Reactions with halogens [2] and methyl iodide [3] paralleled those of the mercury analogue and showed that the $\cdot SCF_3$ group can be transferred intact. Thus, with excess of chlorine, trifluoromethylsulphenyl chloride and silver chloride resulted. With excess of the silver compound bistrifluoromethyl disulphide was also formed. The latter compound was the only volatile product of reaction with excess of bromine or an equivalent quantity of iodine. Excess of methyl iodide gave methyl trifluoromethyl sulphide at 20°. With excess of trimethylsilyl chloride, conversion into silver chloride was lower (64%) and trimethylsilyl fluoride was isolated. Trifluoromethyl trimethylsilyl sulphide was probably first formed; its decomposition to trimethylsilyl fluoride would parallel that of silyl

[1] Man, Coffman, and Muetterties, *J. Amer. Chem. Soc.*, 1959, **81**, 3575.
[2] Haszeldine and Kidd, *J.*, 1953, 3225; Emeléus and Pugh, *J.*, 1960, 1108.
[3] Downs and Emeléus, unpublished work.

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trifluoromethyl sulphide to silyl fluoride.[4] The reaction of trifluoromethylthiosilver with inorganic and organic halogen-containing compounds offers the advantage of the quantitative formation of silver halide. This simplifies the interpretation of the results of conductimetric titrations, a number of which will be reported in a later communication.

Experimental

Preparation of Trifluoromethylthiosilver.—In a typical experiment, dry silver fluoride (14·88 g.) and dry " AnalaR " carbon disulphide (15 ml.) were heated for 12 hr. in a steel autoclave (300 ml.) at 140°. The infrared spectrum of the volatile products showed the presence of carbonyl oxysulphide and silicon tetrafluoride, formed by reaction of primary products with glass, and of carbon disulphide. The black involatile residue (10·50 g.) was extracted with dry acetone, which was removed *in vacuo* at 20°. The last traces of solvent were removed at 70° during 5 hr. The product was trifluoromethylthiosilver (6·50 g., 79%) (Found: C, 5·9; Ag, 51·0; S, 15·0. Calc. for $CAgF_3S$: C, 5·7; Ag, 51·6; S, 15·3%). Silver was estimated as chloride after decomposition of the compound with 1 : 1 nitric acid, and sulphur as sulphate after fusion in a Parr bomb with sodium peroxide, potassium nitrate, and sucrose.[5]

Reactions of Trifluoromethylthiosilver.—(*i*) *With pyridine.* The compound (0·082 g.) was dissolved in dry " AnalaR " pyridine (*ca.* 2 ml.). The solvent was removed *in vacuo* at 0° and the crystalline residue dried to constant weight at 25°. The *adduct* $2AgS{\cdot}CF_3,C_5H_5N$ remained (Found: C, 16·5; H, 1·6; Ag, 43·7; N, 2·6; S, 12·7. $C_7H_5Ag_2F_6NS_2$ requires C, 16·9; H, 1·0; Ag, 43·4; N, 2·8; S, 12·9%).

(*ii*) *With dimethylamine.* No apparent reaction occurred on shaking the silver compound (0·186 g.) with dimethylamine (29 g.) in a sealed tube at 20° (24 hr.). Removal of the solvent at 20° *in vacuo* to constant weight gave a dark brown residue of $2AgS{\cdot}CF_3,Me_2NH$ (Found: C, 10·2; H, 1·6; Ag, 46·3; N, 3·1; S, 14·3. $C_4H_7Ag_2F_6NH_2$ requires C, 10·4; H, 1·5; Ag, 46·6; N, 3·0; S, 13·9%).

(*iii*) *With chlorine.* The silver compound (0·286 g.) reacted immediately with excess of chlorine at 20°. Chlorine was removed from the volatile products by shaking them several times with dry iodine (0·65 g.) and removing residual volatile material at −95° to minimise evaporation of iodine chlorides. Repeated trap-to-trap distillation gave *trifluoromethanesulphenyl chloride*, which was involatile at −131° (0·134 g., 72%) (Found: *M*, 131. $CClF_3S$ requires *M*, 137). The infrared spectrum confirmed this identification. The involatile residue on extraction with acetone gave unchanged trifluoromethylthiosilver (0·018 g.), identified by its infrared spectrum. Extraction with 1 : 1 nitric acid then left silver chloride (0·181 g., 92·5%). With 0·448 g. of the silver compound and 0·145 g. of chlorine the products were bistrifluoromethyl disulphide (0·066 g., 16%) (*M*, 201), trifluoromethanesulphenyl chloride (0·134 g., 80%) (*M*, 138), and silver chloride (0·261 g., 89%).

(*iv*) *With bromine.* Trifluoromethylthiosilver (0·226 g.) was left in contact with bromine (0·317 g.) for several days at 20°. The products identified were *bistrifluoromethyl disulphide* (0·074 g., 68%) (Found: *M*, 203. Calc. for $C_2F_6S_2$: *M*, 202) (the infrared spectrum confirmed this identification), silver bromide (0·113 g., 56%), and unchanged silver compound (0·010 g.).

(*v*) *With iodine.* The compound (0·263 g.) and an equivalent quantity of dry iodine (0·160 g.) were placed in opposite limbs of a tube, which was evacuated and sealed. Reaction occurred at once when the solids were mixed at 20°. The products, after several weeks, were bistrifluoromethyl disulphide (0·097 g., 77%) (*M*, 202) (the infrared spectrum confirmed this identification), silver iodide (0·222 g., 75%), and an unidentified mixture of orange and brown solids (0·058 g.).

(*vi*) *With methyl iodide.* The compound (0·205 g.) reacted with methyl iodide (0·295 g.) during several days at 20°. The products were methyl trifluoromethyl sulphide (0·093 g., 82%) (Found: *M*, 116. Calc. for $C_2H_3F_3S$: *M*, 116) (the infrared spectrum confirmed this identification) and silver iodide (0·216 g., 94%).

(*vii*) *With trimethylsilyl chloride.* Trifluoromethylthiosilver (0·184 g.) and trimethylsilyl chloride (0·123 g.) reacted slowly at 20°. The products identified after several days were trimethylsilyl fluoride (0·030 g., 37%) (Found: *M*, 92. Calc. for C_3H_9FSi: *M*, 92) (the infrared

[4] Downs and Ebsworth, *J.*, 1960, 3516.
[5] Wurzschmitt and Zummermann, *Fortschr. chem. Forsch.*, 1950, **1**, 485.

spectrum confirmed this identification), silver chloride (0·081 g., 64%), and unchanged silver compound (0·051 g.).

One of us (D. E. M.) thanks the National Science Foundation for the award of a Post-doctoral Fellowship.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 22nd,* 1960.]

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509. *Tumour Inhibitors from Plant Sources. Part I.*

By B. F. CAIN.

THE continuation of our programme [1] to screen the New Zealand native and naturalized flora for tumour-inhibiting substances has drawn attention to several plants. Acetone extracts of one of the naturalized species *Anthriscus neglecta* Boiss and Rent * (family, Umbelliferae) [Syn. *A. scandicina* (Web) Mansf.] gave materials capable of producing a statistically significant life-extension in mice bearing the acute lymphocytic leukemia L1210 in mice.†

A lignan, " anthricin," had been isolated from the related *A. sylvestris* Hoffm.,[2] and Hartwell and Schrecker [3] have shown the identity of this material with deoxypodophyllotoxin. *A. neglecta* has also given deoxypodophyllotoxin (0·006% of total plant) and this compound accounts for over 60% of the toxicity of the original extracts.

As a guide in designing fractionation procedures reversed-phase paper-chromatography was used. Tetracyanoethylene [4] gave a range of colours with non-phenolic lignans and as a detecting agent on paper strips is more convenient and sensitive than the reagent described by Jorgenson and Kofod.[5]

Experimental.—Finely ground whole plant (4·4 kg.) was extracted with successive quantities of cold acetone (40 l. total), the extracts being evaporated *in vacuo* to yield a green tar (280 g.). This was shaken with water (2 l.) and chloroform (6 × 1 l.), and the extracts were dried (Na_2SO_4) and evaporated (62·4 g.). The solid was dissolved in aqueous methanol (85% v/v; 1 l.) and extracted with light petroleum (b. p. 60—80°; 3 × 400 ml.). The petrol extracts on evaporation gave non-toxic waxes (43·2 g.) which were discarded. To the aqueous methanol solution, neutral lead acetate (20 g.) in 85% aqueous methanol plus acetic acid (2 ml.) was added, the precipitate removed, and the aqueous solution evaporated to half volume. After addition of an equal volume of water toxic material (12·9 g.) was removed by extraction with ethyl acetate (4 × 500 ml.).

A column of Celite (dried at 110°; 100 g.) containing propylene glycol (55 ml.) was prepared in light petroleum. The active fraction was applied to the column in benzene–light petroleum (1 : 1), elution with this mixture being continued for 2 l. followed by benzene. The eluted fractions (50 ml.) were grouped according to paper-chromatographic evidence, and those containing material of R_f 0·93 (see below) were combined and evaporated after being washed free from propylene glycol with water. Crystallization was effected first from toluene then aqueous ethanol, deoxypodophyllotoxin (0·246 g.) being obtained as prisms, m. p. and mixed m. p. 167·5—168°, $[\alpha]_D^{18}$ −114° (c = 1, in $CHCl_3$) (Found: C, 66·5; H, 5·4. Calc. for $C_{22}H_{22}O_7$: C, 66·3; H, 5·6%). Paper chromatograms also failed to distinguish this and authentic material.[3] Isomerization [3] gave deoxypicropodophyllotoxin, m. p. 171—172°, $[\alpha]_D$ +31° (in $CHCl_3$) (Found:

* Samples were identified by Dr. R. Cooper of the Auckland Institute and Museum, Herbarium number 46,543.

† The author is indebted to Dr. J. F. Burton of these laboratories for details of the biological tests.

[1] Cain, *J.*, 1961, 936.
[2] Noguchi and Kawanami, *J. Pharm. Soc. Japan*, 1940, **60**, 629.
[3] Hartwell and Schrecker, *J. Amer. Chem. Soc.*, 1954, **176**, 4034.
[4] Tarbell and Huang, *J. Org. Chem.*, 1959, **24**, 887.
[5] Jorgenson and Kofod, *Acta Chem. Scand.*, 1954, **8**, 941.

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C, 66·0; H, 5·5. Calc. for $C_{22}H_{22}O_7$: C, 66·3; H, 5·6%). The m. p. was not depressed by a sample prepared from authentic deoxypodophyllotoxin.

Paper chromatography. Whatman's No. 1 discs (27 cm. diam.) were dipped in a solution of propylene glycol in acetone (40% v/v) excess of solvent was blotted off, and the papers were dried in air for 10 min. Spots were applied and the papers were developed radially with benzene saturated with propylene glycol. When developed, papers were oven-dried and sprayed with a 1% solution of tetracyanoethylene in freshly distilled acetone. Typical R_f values were: podophyllotoxin, 0·01 (purple); deoxypodophyllotoxin, 0·93 (purple); α-peltatin, 0·09 (blue); β-peltatin, 0·54 (purple); matairesinol, 0·44 (blue).

The author is grateful to Dr. J. L. Hartwell, Cancer Chemotherapy National Service Centre, Bethesda, U.S.A., for authentic samples of the lignans. This research was totally supported by the Auckland Division of the New Zealand Branch of The British Empire Cancer Campaign Society (Inc.).

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